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THE EPITHELIA OF THE PREGNANT CERVIX*

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FROM reports in the literature one would assume that pregnancy causes specific and characteristic changes in the epithelia of the cervix uteri. For example, Stieve, Hofbauer, and Levey have each described similar changes in the endocervical columnar epithelium; these changes were listed as reduplication or stratification of the lining epithelial cells, plus hyperplastic intraglandular changes. Thus, there is agreement relative to changes which may be encountered in the endocervical epithelium. There also seems to be fair agreement that pregnancy causes specific changes in the stratified squamous epithelium of the external cervix. The exact character of these changes is, however, most indefinite, while Murphy and Herbut have found no particular change other than a thickening. Sheets, Footer, Fluhmann, and others have all alluded to changes in the epithelium of the portio vaginalis which could lead to confusion in the diagnosis of carcinoma. This question of the diagnosis of carcinoma, and more particularly of preinvasive carcinoma, in the pregnant cervix is one which cannot be divorced from a study of presumed specific changes in the cervix attributable to pregnancy, for it has been stated by one authority that because of these "changes" the diagnosis of early carcinoma of the cervix in pregnancy must be made with great hesitation, unless there is gross as well as microscopic evidence of malignancy.

Materials and Methods

Specimens from 96 patients were studied. Sixty-four had grossly "normal" appearing cervices. Cervices were considered normal if there were no extensive or inflamed eversions or "erosions," and no polyps or raised lesions of any kind. In 10 the tissue studied was from total hysterectomy specimens; in each instance

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the indication for the hysterectomy was disease other than that in the cervix. The cervices of the remaining 54 patients were studied by means of punch biopsies. These were obtained chiefly from patients in the prenatal clinics of the Chicago Maternity Center, although the biopsies taken immediately postpartum were from Wesley Memorial Hospital. Routinely the first biopsy was taken at 12 o'clock, but multiple biopsies at two or three different sites were taken from those patients whose original sections showed any unusual features. Thus, from the 54 "biopsy patients" there was a total of 69 specimens, removed at 62 different periods of gestation. An attempt was always made to include the squamocolumnar junction in the biopsies.

The remaining 32 patients had some gross lesion on the cervix. The nature of these lesions will be described when the individual cases are discussed. Twenty-nine of these patients were from the prenatal clinic at the Chicago Maternity Center, one was seen at the Northwestern University clinics, and the remaining two were biopsied by private physicians who sent the specimens to the Laboratory of the Department of Obstetrics and Gynecology of Northwestern University for evaluation. Five of the 32 ultimately were subjected to abdominal complete hysterectomy because of the cervical lesions, and these specimens also will be described later. The biopsies in these cases with gross lesions total 47, of which 39 were taken at different periods in pregnancy.

All sections in both groups of patients were stained with hematoxylin and eosin. The biopsy specimens were fixed immediately in Bouin's fluid. The hysterectomy specimens were also fixed immediately, but in 10 per cent formalin. It is our opinion that Bouin's fixative is superior for a study of this type since it results in better nuclear detail.

Because it was found difficult and time-consuming to control bleeding from biopsy sites in pregnant cervices by means of silver nitrate, Negatan, electrocautery, etc., the last 53 of our biopsies were managed differently. A lamb's wool tampon measuring approximately 8 by 4 by 4 cm. was placed in the vagina and pressed firmly against the cervix immediately after the biopsy was taken. This was done often in the face of fairly brisk bleeding from the biopsy site. The patient was then instructed to remove the tampon in 4 to 6 hours and report any bleeding, other than minimal spotting. The 53 cases so treated included 7 with biopsies taken from three sites on the cervix, and 6 with gross lesions. Not a single patient reported bleeding other than slight spotting, after removal of the tampon. There have been no cases of abortion, premature labor, or other undesirable complications following these biopsies.

During the period of this study (16 months), sections from approximately 1,974 "control" nonpregnant cervices have also been studied. These include sections from the cervices of 1,600 total hysterectomy specimens, both from Passavant Memorial Hospital and Wesley Memorial Hospital, where a total hysterectomy rather than a subtotal is routine. The majority of these, therefore, represent grossly "normal" cervices.

The remaining 374 specimens were biopsies from grossly abnormal cervices of nonpregnant patients, which had been sent to the departmental laboratory for evaluation.

More recently 50 consecutive biopsies from *nonpregnant* patients have been studied to determine the incidence of those changes in endocervical epithelium which were listed by Hofbauer as specifically caused by pregnancy.

Findings

I. Pregnancy With No Gross Lesion.—

The stratified squamous epithelium of the portio vaginalis and the epithelium of the endocervical canal and glands will be discussed separately. To

simplify the tabulations, findings in the first biopsy or in the first slides from a surgical specimen will be used, whereas significantly different repeat biopsies will be discussed separately.

A. Stratified Squamous Epithelium.—

There is some confusion in the literature between the terms "stratum basalis" and the "basal-cell layer." Actually, the basal-cell layer consists of one distinct layer of cuboidal or more often columnar cells with relatively large nuclei; their long axis is perpendicular to the basement membrane and to the underlying stroma. On the other hand, the stratum basalis consists of the basal-cell layer plus the cells of the stratum spinosum which overlie it; the cells of this latter layer have a polyhedral form with distinct intracellular bridges. Their nuclei are still relatively large but not as large as in the basal layer. The cells immediately superficial to this layer have a moderately flattened outline with somewhat small nuclei, and, finally, the cells of the stratum corneum are markedly flattened and contain small pyknotic nuclei.

No squamous epithelium was present in 4 of the initial 64 biopsies. There remain 60 biopsies for study with the following trimester of gestation distribution:

0-14 weeks	6
15-28 weeks	23
29-40 weeks	31

1. Thickness: The relative thickness of the epithelium was estimated in each specimen (in comparison with that of the average nonpregnant female of comparable age). In this, care was taken to discount or allow for areas where the epithelium was sectioned tangentially. The estimates are tabulated in Table I. Thirty per cent of the total seemed no thicker than in the average nonpregnant patient. A little more than one-half fell in the group "slight or moderately thickened." Many of those from nonpregnant cervices would, of course, fall in a similar group. Marked increase in thickness occurred in a minority of patients and only in the second and third trimester. No conclusion can be drawn from this occurrence, however, because of the small number of cases in the first trimester. The increased thickness, where apparent, seemed to involve all layers of the stratified squamous epithelium.

TABLE I. THICKNESS OF STRATIFIED SQUAMOUS EPITHELIUM

PERIOD OF GESTATION	NUMBER OF SPECIMENS	PER CENT "AVERAGE" NONPREGNANT THICKNESS	PER CENT SLIGHT OR MODERATELY THICKENED	PER CENT MARKEDLY THICKENED
0-14 weeks	6	50.0	50.0	
15-28 weeks	23	26.1	56.5	17.4
29-40 weeks	31	29.0	64.5	6.5

2. Architecture, polarity: There were no variations from the normal in 54 of the 60 cases. One of the remaining showed widening of the rete pegs; another had a moderate basal-cell hyperplasia. In two there were small areas where the architecture of the lower half of the epithelium was distorted and nuclear variability was present. No abnormal mitotic figures were seen. Repeat multiple biopsies in each of these two showed no abnormalities. In the remaining two a diagnosis of well-differentiated preinvasive squamous-cell carcinoma was made on the original and repeat biopsies. The abnormal epithelium extended over most of the surface, and nuclear abnormalities were marked. Mitotic figures were seen in all layers, and some of these were abnormal in configuration.

3. Basal layer and mitoses: The majority of specimens had the normal one-cell basal layer. An increase in layering of the basal cells which seemed significant, i.e., was more than an isolated minute area or due to tangential section of the tissue and covered a considerable portion of the slide, occurred in 18 of the 60 cases, or 30 per cent. Arbitrarily, if the area seemed to cover more than 20 per cent of the section, it was included in this group which ultimately totaled 18. Of these 18, 7 were from the second trimester, and 11 from the third trimester. The epithelium in 16 of the 18 showed some degree of thickening, while two were of average thickness.

The thickness of basal cells in this group was limited to an increase to 2 to 4 cell layers. The nuclei maintained normal polarity and were uniform in size, shape, and staining. Mitoses were not unusually frequent either in this group or in specimens which showed the usual one-cell basal layer. Mitoses were seen only in or very close to the basal layer. The process just described must be distinguished from pathologic basal-cell hyperplasia where the lower one-third to one-half of the epithelium is involved, with varying degrees of anaplasia, and with mitotic figures present some distance away from the basement membrane.

4. Nuclei, nucleoli, and chromatin: Except for the nuclear variabilities already discussed, no abnormalities were noted. The normal nucleocytoplasmic ratio was maintained, nucleoli though occasionally multiple were not unusual, and the chromatin was normal in amounts and distribution.

B. Endocervix.—

No endocervix was present in the original biopsies from 5 of the 64 normal cervices. There remained 59 biopsies for study, with the following distribution according to trimesters of pregnancy:

0-14 weeks	7
15-28 weeks	24
29-40 weeks	28

1. Epidermization: Epidermization, or "squamous" metaplasia, occurred either at the squamocolumnar junction, or in the endocervical canal, in 32 of the 59 specimens, or 54.2 per cent. The degree of epidermization varied from a tiny patch to considerable areas covering up to 75 per cent of the endocervical canal as seen in the biopsy specimen; these findings are tabulated in Table II.

TABLE II. ENDOCERVICAL EPITHELIUM IN CERVICES WITH NO LESIONS

	0-14 weeks	15-28 weeks	29-40 weeks	TOTAL
Number of cases	7	24	28	59
Epidermization	2	9	21	54.2%
Stratified columnar epithelium	2	7	10	32.2%
Intraglandular hyperplasia	1	3	10	23.7%

There was much variation both in the extent and the thickness of the metaplastic epithelium. In its simplest form this aberrant epithelium was 2 to 3 cell layers thick, while at its maximum it was 10 to 12 cell layers in thickness. While this process is loosely spoken of as "squamous" metaplasia, the resultant epithelium in the nonpregnant as well as the pregnant cervix most frequently resembles transitional epithelium rather than true stratified squamous epithelium, since in most instances there is no flattening or "squamification" of the superficial layers of cells.

Nuclear polarity in this metaplastic epithelium was only fairly well maintained and was obviously distorted in 15 of the 32 cases. A similar lack of

nuclear polarity has been seen in nonpregnant cervices and although we do not have exact and tabulated data, it is our impression that the frequency of this finding is approximately the same as in pregnant cervices. The nuclei generally were uniform in size, shape, and staining qualities. In 5 of the 32 cases the nuclei showed moderate variability in these latter properties, but this, too, is occasionally seen in nonpregnant cervices. Mitoses were infrequent, appearing in only 7 of the 32 specimens. Most instances of epidermization were obviously benign by all of our present concepts. Even in those with distorted polarity and some variability in nuclear size and shape, the findings were not sufficient to justify a diagnosis of malignancy. Mitotic figures, though seen some distance away from the basement membrane, were normal and the nuclear variability did not include marked hyperchromatism, bizarre shapes, or giant nuclei. Normal nucleocytoplasmic ratio was fairly well preserved.

Fig. 1.—Stratified columnar epithelium in endocervical canal from patient 6 weeks pregnant.

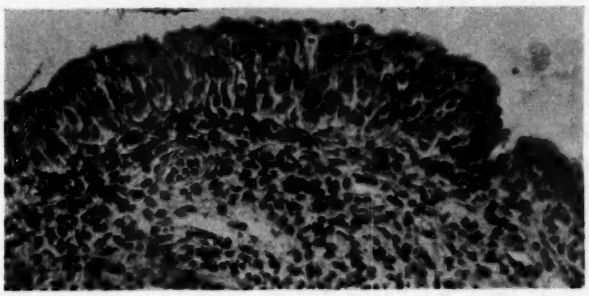

Fig. 2.—Stratified columnar epithelium in endocervical canal from nonpregnant patient. Note similarity to Fig. 1.

2. Endocervical epithelium: We have observed variations from the usual simple tall columnar epithelium of the endocervical canal. In fact, these changes were similar to the hyperplastic changes which Hofbauer described. The variation where present was actually a multilayering of the columnar epithelium. It varied in degree from two cell layers in thickness with each cell maintaining its columnar shape, to a multilayered epithelium 5 to 6 cell layers in thickness projecting into the endocervical canal. In this latter type the superficial cells were columnar, the remainder round or polyhedral. Vertical

polarity was usually well maintained and there was a minimum of nuclear variability. In actual fact, the best histologic term for such an epithelium would be "stratified columnar." Intraepithelial vacuoles of varying sizes were frequent. These vacuoles would necessarily distort some of the cell outlines, but the over-all stratified columnar appearance was obvious. Mitotic figures were rare and no abnormal relationships between the most basal cells and the underlying stroma were noted. The incidence of this hyperplastic process is noted in Table II.

Fig. 3.

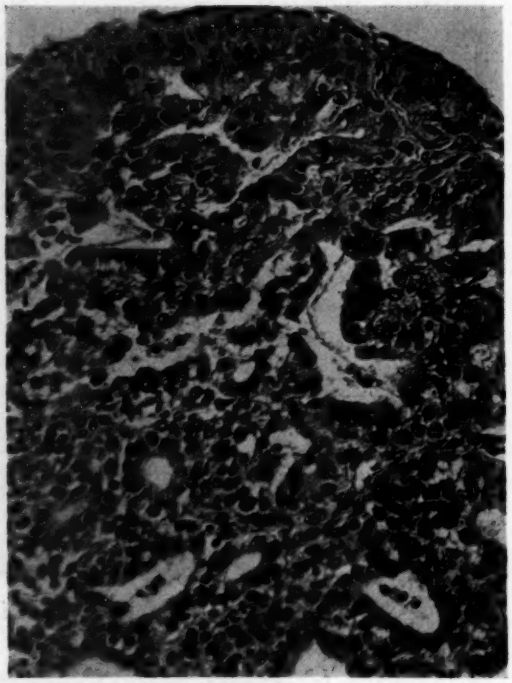

Fig. 4.

Fig. 3.—Marked intraglandular hyperplasia in endocervical gland from patient 30 weeks pregnant. The stratified squamous epithelium is of average thickness and shows no abnormalities.

Fig. 4.—Intraglandular hyperplasia from nonpregnant patient. No typical epithelial pattern exists.

As seen from this table, some degree of stratified columnar epithelium was seen in 32 per cent; this change was found in all three trimesters, although it appeared to be more common in the second and third. The extent of this process varied from a small isolated patch to an extensive area covering most of the endocervical canal present in the section. However, such extensiveness was not limited to the third trimester. As previously stated, most of the specimens being discussed here were obtained by biopsy. They, therefore, represent only a small sample of the endocervix. If larger samples were available a much higher incidence of these changes might be found. No conclusion can be drawn from these data regarding the actual incidence of these changes in the pregnant cervix.

It is of interest, however, that in the series of 50 consecutive biopsies from nonpregnant patients 8, or 16 per cent, had a greater or lesser degree of identical changes in endocervical surface epithelium. Therefore, although it is possible that these changes are more common during pregnancy they certainly are not specific to pregnancy.

This hyperpalstic phenomenon which we have observed in some pregnant cervices is obviously benign; it has none of the characteristics of malignancy. This process is easily distinguishable from the usual epidermization, and, in fact, the two may exist side by side on a given slide.

3. Endocervical glands: One can obtain only a rough estimate of the degree of development of glands from the biopsy material in this study. However, only 5 of the cases in the third trimester and 4 in the second trimester showed much greater than an average abundance. Epithelial alterations from the usual simple columnar type were also noted in the glands; in some spots there appeared

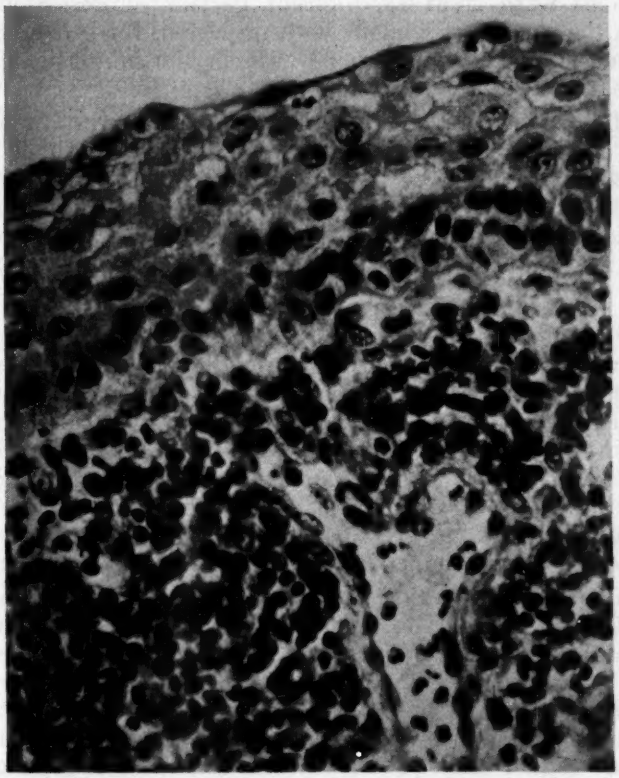

Fig. 5.—Area of epidermization in endocervical canal from patient 32 weeks pregnant. There is moderate loss of nuclear polarity but the individual nuclei are essentially normal.

typical 2 to 5 cell layered stratified columnar epithelium just as had been observed in the endocervical canal. However, more characteristically there appeared in some specimens a phenomenon which can best be described as intraglandular hyperplasia. In its extensive form the proliferation of epithelial elements almost occluded the gland lumen. Only the most basal one to two cells maintained their polarity with the underlying stroma. Numerous vacuoles, both large and small, were usually present and intermingled with the epithelial cells so that no typical epithelial pattern existed. The epithelial cells themselves often consisted of only a small, dark-staining nucleus with scant cytoplasm, the remainder of the cytoplasm being replaced by a vacuole. Many of the cells could not be identified as columnar. The remaining nuclei were uniform in size and shape, and mitotic figures were infrequent. The incidence of this intraglandular hyperplasia is noted in Table II. Apparently it increases in the last trimester, as it was noted three times more frequently than in the second trimester.

The over-all incidence of intraglandular hyperplasia was 23.7 per cent. As in the hyperplastic changes observed in the lining of the endocervix, there is no reason to suspect malignancy from the microscopic appearance of this intraglandular hyperplasia. It is not limited to pregnancy. Similar intraglandular hyperplasia was noted in 12 per cent of the 50 consecutive biopsies from *nonpregnant* patients. In these particular specimens a total of 22 per cent had either intraglandular hyperplasia, or stratified columnar surface epithelium, or both.

II. Cervices With Gross Lesions.—

The specimens were from 43 different periods of gestation and from 32 patients. As in the case of specimens with no lesion, for purposes of simplification, findings in the first biopsy will be used in the tabulations as well as the trimester of pregnancy at that time.

The type of gross lesion varied considerably. This was further complicated by the fact that they were described differently at different times and by various clinicians. However, generally they can be divided into 4 hypertrophic, or definitely elevated thickened lesions in the squamous epithelium, 24 large or inflamed "erosions," one ulcer, and three condyloma-like papillomas. Only 4 of these 32 patients had symptoms; 3 had pinkish discharge and one vaginal spotting.

A. Endocervix.—

Because it will be possible to combine our findings in endocervical elements of cases with and without lesions, these will be discussed before considering the stratified squamous epithelium. In thirty-one of the 32 cases there was endocervical tissue in the sections but in only 29 sufficient to permit an adequate description. Generally speaking, the extent of glands was much greater in these biopsies than in those obtained from patients with no lesion. Seventeen of the 29 had glandular elements greatly in excess of the average. This is to be expected when one notes that the majority of these lesions were "erosions."

1. Epidermization: Epidermization was also frequent in this group, occurring in 14 of 29 specimens, or 48.3 per cent. Combined with the incidence in the cases with no lesions, the total over-all incidence was 46 of 88 specimens, or 52.3 per cent. These findings are tabulated in Table III. The variants noted previously occur in about the same ratio here as in specimens from cervices with no lesion. This high incidence of epidermization, in 52.3 per cent of all specimens, is probably higher than in the nonpregnant state, although we have no definite data on this point.

TABLE III. ENDOCERVICAL EPITHELIUM IN CERVICES WITH LESION, AND TOTAL CASES

	0-14 WEEKS		15-28 WEEKS		29-40 WEEKS		
	CERVICES WITH LESION	TOTAL CASES	CERVICES WITH LESION	TOTAL CASES	CERVICES WITH LESION	TOTAL CASES	TOTAL
Number of cases	6	13	14	38	9	37	88
Epidermization	3	5	6	15	5	26	52.3%
Stratified columnar epithelium	1	3	5	12	8	18	37.4%
Intraglandular hyperplasia	3	4	5	8	5	15	30.7%

2. Endocervical epithelium: The incidence of stratified columnar epithelium in this group and the combined group is shown in Table III. There is probably no significant difference between the incidence in the two groups. The over-all incidence was 33 of 88 cases, or 37.4 per cent.

3. Endocervical glands: The incidence of intraglandular hyperplasia in this group as shown in Table III was 44.8 per cent. The over-all incidence was 30.7 per cent.

B. Stratified Squamous Epithelium.—

Twenty-nine of the 32 cases with cervical lesions were from patients who were seen at the prenatal clinics of the Chicago Maternity Center from Oct. 1, 1948, to Feb. 1, 1950, during which time a total of 2,249 new prenatal patients were seen in this clinic. In 7 of the 29 patients with cervical lesions a microscopic diagnosis of preclinical (preinvasive) squamous-cell carcinoma was made. No case of invasive carcinoma was seen. The incidence of carcinoma then in a large group of pregnant patients in which only suspicious looking cervices were investigated was 7 of 2,249, or 0.31 per cent. This, of course, does not represent the true incidence of carcinoma in the clinic because relatively few of the grossly normal-appearing cervices were biopsied, and two carcinomas, as judged by our present stadards of diagnosis, were found in this "normal cervix" group.

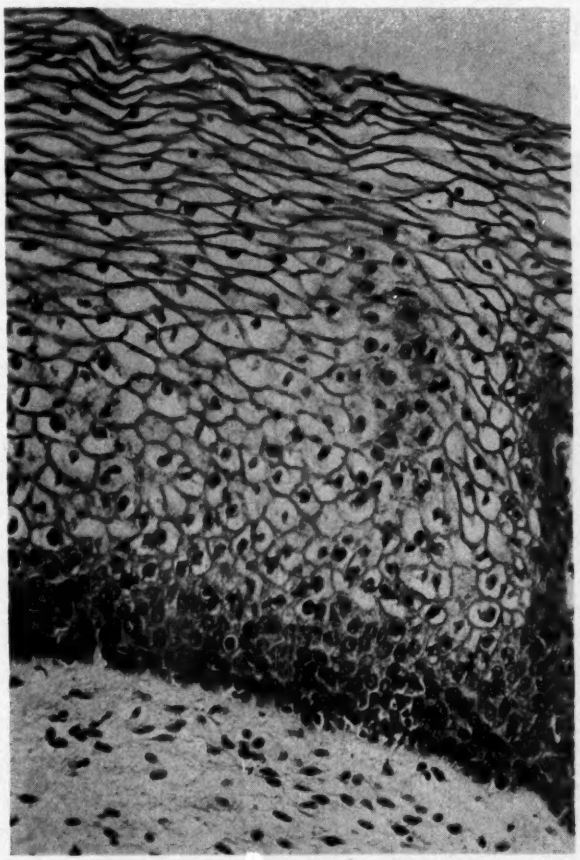

Fig. 6.—Moderate over-all thickening of stratified squamous epithelium associated with an increase in the basal layer. The nuclei are normal.

Two of these patients with preclinical carcinoma were treated by abdominal complete hysterectomy within two weeks after the diagnosis was made, i.e., at 14 and 24 weeks. The identical lesion was found in the surgical specimen as was seen in the biopsy. Two patients had a cesarean hysterectomy at 38 weeks; the diagnosis of cancer had been made at 8 and 22 weeks, respectively. In both of

these, the lesion was present in the surgical specimen, and it apparently was still preinvasive. One patient who was biopsied at term has refused follow-up care, and another was in the third trimester at the time of writing.

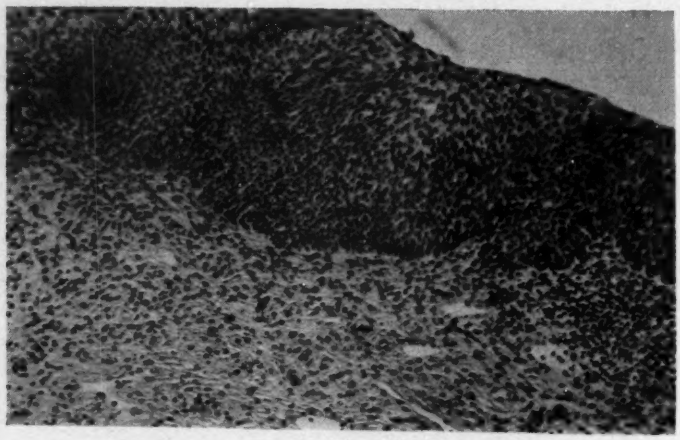

Fig. 7.—M. H. Undifferentiated preinvasive carcinoma from patient 8 weeks pregnant. Abnormal cells are present throughout the entire thickness of the epithelium.

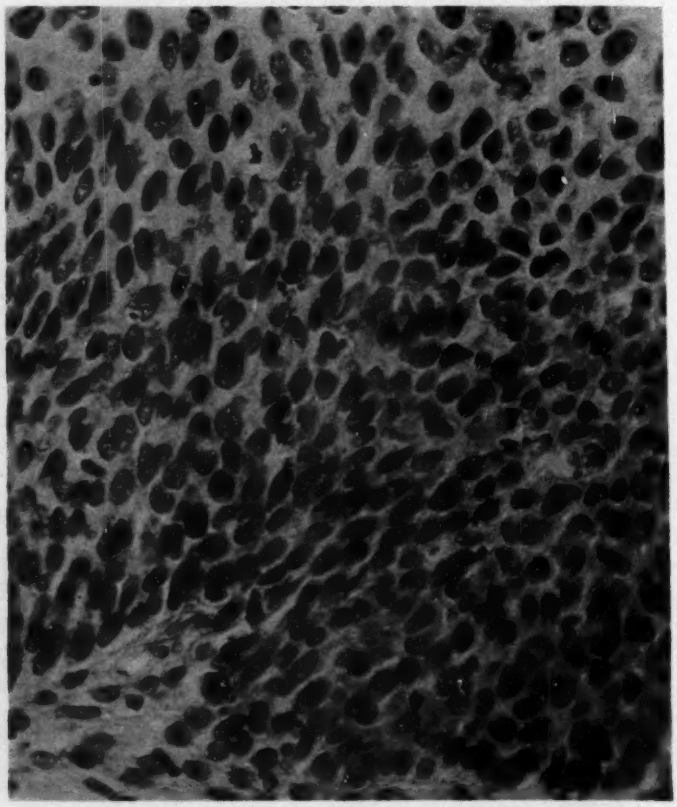

Fig. 8.—High power of Fig. 7. There is complete loss of architecture and polarity. Mitotic figures are present in all layers of the epithelium.

Of the two remaining patients, one who was biopsied at term had an abdominal complete hysterectomy a few months later; the patient was 10 weeks

pregnant at this time. One small area had some nuclear variability and distortion of architecture, but the findings were considered insufficient for the diagnosis of carcinoma in the hysterectomy specimen.

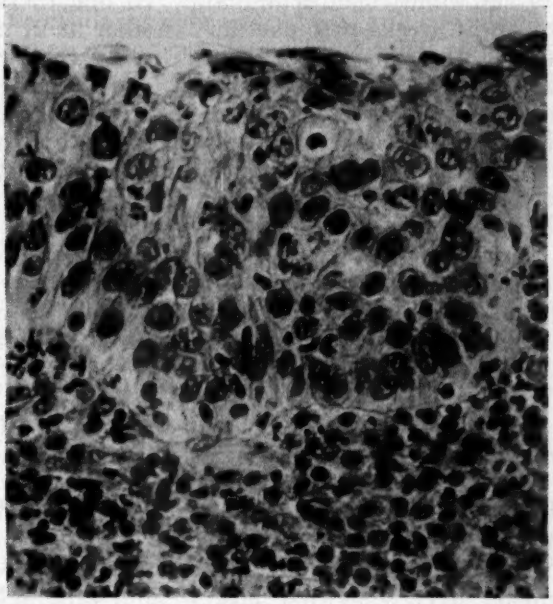

Fig. 9.—D. W. Biopsy specimen of preinvasive carcinoma from patient 22 weeks pregnant. The nuclei show marked variation in size and shape. Normal architecture is lost.

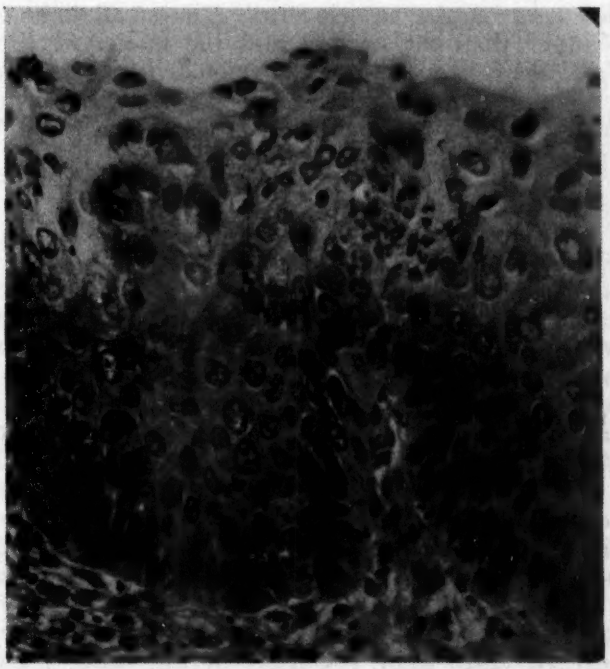

Fig. 10.—D. W. Surgical specimen at 24 weeks from same patient as in Fig. 9. A similar preinvasive carcinoma is present.

The final patient had a biopsy diagnosis of preinvasive carcinoma at 30 weeks of gestation. The patient delivered spontaneously and made herself unavailable for follow-up study until six months post partum. Biopsy at this time showed a lesion identical to that noted during pregnancy, apparently still preinvasive.

Three patients had condyloma acuminata. In one there were biopsies at 28 weeks, 29 weeks, and 6 weeks post partum; another at 27 and 29 weeks; and a third was biopsied at the time of delivery. Grossly the two condylomas followed prenatally seemed to grow markedly during pregnancy. The microscopic appearance was similar in all three. The epithelium was markedly thickened and thrown into papilla-like folds; very wide rete pegs and heavy cornification were present. Polarity was fairly well preserved and architecture was generally normal. The nuclei throughout were large, although there was no abnormal variation in their size or shape. Nucleoli were prominent and occasionally multiple; mitoses, though frequent, were normal in configuration and situated in or near the basal layer. The basal layer was predominantly one cell layer in thickness. The specimen studied six weeks post partum showed disappearance (apparently spontaneous) of the condylomatous areas with an intense inflammatory reaction in denuded tissues.

Three of the remaining cases show some variation from the usual stratified squamous type: one from a patient 32 weeks pregnant with a "hemorrhage-like" lesion on the anterior lip had in most areas a basal layer which seemed 2 to 4 cell layers in thickness, although the epithelium was not noticeably increased in total thickness. There were no nuclear variabilities. The second from a patient 33 weeks pregnant with an eroded area on the anterior lip of the cervix had a small area of epithelium where the architecture was distorted in the lower half. Here the nuclei were somewhat larger, and, although there was little variation in size, a few giant forms were seen. Mitotic figures were frequent, but not abnormal. Repeat biopsies one week later at 2, 10, and 6 o'clock showed no abnormalities. The third was from a patient 24 weeks pregnant who had a reddened, eroded area on the anterior lip. The small area of epithelium in question was thinner than the normal and the nuclei were uniform in size, tightly packed and the cells maintained poor polarity. The basal layer was not discernible as such. Nucleoli and chromatin were prominent, mitoses were frequent but not abnormal. A diagnosis of active basal-cell hyperplasia was made, and the patient is being followed post partum.

Comment

Pregnancy Changes in the Cervical Epithelium.—

In presenting our data we have endeavored to differentiate and to separate findings in the stratified squamous epithelium of the external cervix from those in the endocervical epithelium. Unfortunately, this has not been common practice in reports from the literature. Hyperplastic changes in the endocervical epithelium have been described by some previous workers and have been referred to by other workers as hyperplastic changes in the "cervical" epithelium without stating whether they occurred in squamous, or in columnar epithelium, or in both.

Actually, changes in the stratified squamous epithelium of the external cervix are minimal and inconstant. In our series, the squamous epithelium in cervices with no gross lesion was markedly thickened in only a few specimens. In 30 per cent the basal-cell layer was thickened to a modest degree, and the majority of cases which showed an increase in basal layer also had an over-all moderately thickened epithelium. Similar findings have been noted in non-pregnant cervices, but, unfortunately, we do not have exact data as to their incidence. Even if it were granted that these thickenings are more common in

the pregnant cervix, they certainly cannot be considered as a change specific to pregnancy. Furthermore, they are not found with sufficient frequency to be considered characteristic of pregnancy.

Endocervical "hyperplastic changes" include formation of stratified columnar surface epithelium as well as intraglandular piling-up of epithelium. These changes have been considered characteristic of and specific to pregnancy. In our series of 88 pregnancy specimens with endocervical elements, we have observed one or both of these changes in 44.4 per cent. As previously stated, one or the other of these changes was found in 22 per cent of 50 consecutive biopsies from nonpregnant patients. It is true that such changes are probably more widespread, as well as more frequent in the pregnant than in the nonpregnant cervix. But even so, such changes are seen sufficiently often in the nonpregnant, so that they can no longer be considered either specifically due to pregnancy or specifically limited to the pregnant cervix.

Actually we were not surprised that our studies failed to reveal changes either in the squamous or columnar epithelium of the cervix, or in its glands, which could undeniably be attributed to pregnancy or identified as the direct result of pregnancy. Despite earlier claims to the contrary (Wollner; Sjovall; Papanicolaou, Traut and Marchetti), recent efforts have also failed to demonstrate constant cyclic changes in crevical epithelium which lend themselves to accurate correlation with the cyclic changes in the endometrium (Atkinson, Shettles and Engle; Topkins; Bradburn). Consequently one might assume that the epithelial elements of the cervix are relatively refractory in histologic appearance (not function) to variations in hormonal stimulation.

What can be said about making the diagnosis of pregnancy on the basis of examination of a given section of cervix? A decidual reaction in stromal cells and a marked increase in the number and size of blood vessels are sufficient evidence for such a diagnosis (granted that a hydatid mole or chorionepithelioma has been excluded). However, the diagnosis cannot be made with any degree of accuracy on the basis of changes in the epithelia alone. Certainly, duration of pregnancy cannot be estimated from the microscopic changes described; in fact these changes are no more than exaggerations of those found in the nonpregnant cervix. In many pregnant cervices, such changes are minimal and frequently absent. The converse is also true; specimens from nonpregnant cervices have been examined in which similar changes were widespread.

Epidermization or metaplastic transformation of endocervical simple columnar epithelium to transitional or stratified squamous epithelium was a frequent finding in this series of specimens from pregnant patients with or without gross lesions (52.3 per cent). We have no exact data on the subject, but the incidence seems higher than that in the nonpregnant cervix. There are data in the literature as to the incidence of epidermization in cervices. For example, Carmichael and Jeaffreson found it in 41 per cent of 343 cervices. These data, however, were obtained from whole sections of operative or autopsy specimens and are therefore not comparable to ours which are largely from biopsy specimens. It is still a fact, however, that this type of metaplasia certainly is not specific to pregnancy and it is not found in the pregnant cervix alone.

Diagnosis of Carcinoma During Pregnancy.—

There is no confusion in the microscopic diagnosis of the clinically evident carcinoma in the pregnant patient. By the time the carcinoma is grossly evident, microscopic evidences of invasion are extensive and unmistakable. Benign lesions in a pregnant cervix, such as a massive focal decidual reaction, or an ulcerative acute cervicitis, may suggest cancer grossly. In such instances, the microscopic differentiation is accomplished with ease. Neither the clinically evident carcinoma nor these latter lesions will be considered further. The diagnosis of preclinical carcinoma during pregnancy presents a real problem.

The term preclinical carcinoma includes those in which the carcinoma is preinvasive or minimally invasive. The cervix grossly may or may not appear completely normal, but a lesion, if present, cannot be grossly recognized as carcinoma. There is, of course, still doubt in the minds of certain general and special pathologists whether preinvasive, or intraepithelial, carcinoma actually is cancer. By others it is considered an early stage of true cervical carcinoma, and this is the attitude of most who are particularly interested in gynecologic pathology. The exact and detailed criteria for the diagnosis are not pertinent to this discussion. Of necessity, however, the diagnosis is made on the basis of changes in cellular characteristics, particularly those of the nuclei. Unfortunately, minor variations in cellular characteristics are encountered in benign tissues. This is particularly true of endocervical epithelium. Large, bizarre, and hyperchromatic nuclei may be seen in endocervical epithelium when there is acute and chronic inflammation. Usually, however, such nuclei are sparsely located, and the epithelium in general has an obviously benign appearance. Areas of epidermization may cause confusion because of closely packed nuclei with no organized polarity and minor variations in nuclear size and shape. In some instances repeat sections deeper into the block, or reblocking, or repeat biopsies are necessary before a decision can be reached as to whether the process is benign or malignant. These statements, of course, apply to the minority of lesions. *However, they apply equally to the nonpregnant and to the pregnant cervix.* Since it is possible that epidermization is more common in the pregnant than in the nonpregnant, such confusing specimens may be seen a few more times per year in the pregnant than in the nonpregnant cervix. It is still true, however, that the confusion does not arise because of any epithelial change specifically due to pregnancy.

We, therefore, believe that if the criteria are present for the diagnosis of a preinvasive carcinoma, such a diagnosis is valid even though the patient is pregnant.

Summary and Conclusions

1. The stratified squamous and endocervical epithelia from the cervices of ninety-six pregnant women have been studied. Sixty-four of these patients had normal-appearing cervices; thirty-two had some gross lesion on the cervix.

2. Although hyperplastic alterations of the epithelium of the endocervical canal and glands were noted, these changes could not be considered specific to pregnancy since they were frequently seen in nonpregnant specimens also.

3. Epidermization was noted in slightly over half the cases studied. Atypical forms of epidermization are compared and contrasted with the microscopic picture of carcinoma.

4. No typical pregnancy changes were noted in the stratified squamous epithelium. The incidence of hyperactivity as manifested by increased general thickness, increase in basal-cell layer, and frequency of mitoses is discussed.

5. It is concluded that when the criteria for the diagnosis of carcinoma of the cervix are present, this diagnosis is valid irrespective of whether the patient is or is not pregnant.

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303 East Chicago Avenue

Discussion

DR. M. C. WHEELOCK (by invitation).—I have seen this material through the courtesy of Dr. Carrow and Dr. Greene and am convinced of the accuracy of their conclusions. I do not see how anyone will confuse the morphological changes of the pregnant cervix, as presented, with carcinoma in situ. Carcinoma in situ or preinvasive carcinoma is obvious in the slides shown in contradistinction to the changes which are delineated in the pregnant cervix. It is not a difficult problem to solve. Unfortunately, I have not seen many biopsies on the pregnant cervix until now. I have had the good fortune to see a number of preclinical cervical carcinomas.

DR. GEORGE H. GARDNER.—The authors have explained how stupid errors in interpretation of earlier reports have warped the thinking and utterly confused the present-day parlance on this subject. In reality the most freqently quoted early writers were concerned primarily with hyperplastic changes in the endocervical columnar epithelium, and considered them specific for pregnancy; they did not contend that similar hyperplasia also occurs in the squamous epithelium of the portio. Nevertheless, some present-day authorities would have us believe, apparently because they continue to misconstrue those early reports, that certain changes occur both normally and frequently in the squamous epithelium of the pregnant cervix, and that these changes cannot be distinguished with certainty from preinvasive cancer. Isn't it regrettable that such erroneous concepts have crept into current discussions about cervical cancer?

We have seen irrefutable evidence, which demonstrates beyond any question of doubt, that there are no specific pregnancy changes in the several epithelia of the cervix, i.e., none in the columnar epithelium of the canal, none in the glands, and none in the squamous epithelium of the pars vaginalis. In fact, Drs. Carrow and Greene failed to find changes in the endocervix, such as were formerly considered specific for pregnancy, either in the majority of their biopsies or in the majority of their hysterectomy specimens. On the other hand, they have observed these so-called specific pregnancy changes in many nonpregnant cervices.

But these observations should not startle you. Despite the contentions of a scattered few, most gynecological pathologists are unable to recognize cyclic changes in the nonpregnant cervix, i.e., nothing which could possibly be correlated with those universally recognized cyclic changes in the endometrium. All of which probably means that cervical epithelia are relatively unresponsive to any and all physiologic variations in hormone stimulation, certainly in so far as histologic changes are concerned.

Please be assured that this study has much more than mere academic implication; there is also a real practical aspect. I refer to its bearing on the histologic diagnosis of early cancer in the pregnant cervix. Usually this is no problem at all; occasionally it is extremely difficult, but I am sure you must realize that such difficulties occur, and with equal frequency, in a study of sections from the nonpregnant cervix. The authors contend, and I am convinced, that it is totally irrelevant whether the patient is pregnant, or is not pregnant; when the criteria for the histologic recognition of cancer are present, that diagnosis is valid; and the patient should be treated accordingly.

DR. LESTER D. ODELL.—For the last three years we have been studying the activity of the enzyme, β-glucuronidase, in the various gynecologic tissues. The method of measuring the activity of the enzyme is very simple. We have noted that there is a specific difference in activity between benign and malignant cervices. But, in addition, it has been noted that pregnant cervices give us assay values which are increased and which are within the malignant range. This change is not confined to the pregnant cervix at term. It has been observed accidentally in two early pregnancies, discovered after hysterectomy and after curettage. According to one investigator, this enzyme is associated with increased cellular mitoses. It is possible that the morphological changes that occur in some pregnant cervices are responsible for the increased activity of the enzyme. At the Chicago Lying-in Hospital we have not seen many cases of malignancy in pregnant cervices. Sime years ago one of our staff reported 4 in 40,000 deliveries. It is entirely possible that the morphological changes described by Drs. Carrow and Greene are reversible. If so, the entire status of the morphological picture of interepithelial cancer is in some doubt. I do not believe that patients with reversible changes have cancer.

It is a matter of record that Novak recently described the morphology of the pregnant cervix obtained from a large number of cervices of pregnant women. It was his observation that the histologic changes in some of these cervices approached those seen in early cancer. It is significant that the patients did not develop cancer later on.

DR. CHARLES E. GALLOWAY.—I think this is a very stimulating paper and maybe twenty years from now we will be farther along in this problem than we are now. In the present state of our imperfect knowledge concerning so-called carcinoma in situ, even granting that you can make a diagnosis and that the diagnosis is correct, I do not feel that anyone is justified in interrupting pregnancy and removing a woman's uterus on that account. I do not believe that we have progressed far enough to take a baby's life and ruin a woman's reproductive life by taking out a uterus that is pregnant on which a diagnosis of carcinoma in situ has been made. I believe that if a diagnosis of invasive carcinoma can be made by biopsy, we are justified in doing so. I do not believe that we have absolutely settled the fact that so-called carcinoma in situ is an irreversible lesion. I do not quite think that it is progressive every time. There may be a certain number that are retrogressive and I think our knowledge will have to increase tremendously before we can make such a decision as to interrupt pregnancy on that diagnosis at the present time. There is no consistent change in the cervix in pregnancy. I agree with that part of it. One cervix will produce a tremendous hyperplasia and in others you can see no evidence of it whatever.

There is one thing I want to plead for and I did so a year ago in a paper on the pregnant cervix. I want to make a plea that routine inspection of the pregnant cervix should be a part of our prenatal care.

THE EXPERIMENTAL PRODUCTION AND PROLONGED MAINTENANCE OF DECIDUA IN THE NONPREGNANT WOMAN*

EDUARD EICHNER, M.D., F.A.C.S., GEORGE G. GOLER, M.D., JOHN REED, M.D., AND MAURICE B. GORDON, M.D., CLEVELAND, OHIO

(From Cleveland State Hospital and the Division of Obstetrics and Gynecology, Mount Sinai Hospital, Cleveland, Ohio)

EIGHT patients at Cleveland State Hospital were subjects in the research problem† of producing by hormones the pyeloureteral dilatation so common in pregnancy. At the start of the experiment all were normally menstruating women of childbearing age. Four were parous and three were virginal. Pelvic examinations disclosed no gross abnormalities, and preliminary endometrial biopsies verified ovulation. Therapy was started on all patients on the same date, the phase of the menstrual cycle being disregarded. Cervical and vaginal spreads, catheterized bladder-urine sediments, blood counts and blood chemistry determinations, endometrial biopsies, and twenty-four-hour urine examinations were done at intervals. Culdoscopic examination of the ovaries was also done. Clinical signs of early pregnancy (amenorrhea associated with uterine and breast changes and a positive pregnancy test) occurred in each subject.

Material

At the onset of the experiment (D-1‡) each subject received 25 mg. of estradiol by pellet implant, as well as injections of 10 mg. progesterone and 250 units of chorionic gonadotropin. The latter two hormones were given daily, and rapidly increased to 100 mg. and 2,000 units, respectively, per injection. At two-week intervals 50 mg. estradiol were implanted to a total of 275 mg. On D-108 gonadotropin injections were discontinued on one-half the patients (Group 2). Each of these had received 149,000 units. Each member of Group 1A received 254,000 units by D-148 when gonadotropin was discontinued, while the two subjects in Group 1B received 282,000 units before all treatment was stopped on D-162. All subjects received 12,875 mg. progesterone.

Absorption, utilization, and excretion of these hormones varied from patient to patient, and from time to time in the same patient. Estradiol pellets were encapsulated in one subject, and remained palpable throughout the latter half of the experiment. One patient developed abscesses at the sites of the injections. Pregnancy tests[5] were positive at some time on all patients, but became negative within five days after the discontinuance of the gonadotropin.

*This problem was completed only through the active participation of the firms which gave so generously of their supplies:

Chorionic gonadotropin: Ayerst, McKenna and Harrison, C. D. Smith Pharmacal Co., Schering Corporation, and The Upjohn Company.

Diethylstilbesterol: Grant Chemical Company, Inc.

Estradiol: Schering Corporation.

Progesterone: C. D. Smith Pharmacal Co., Schering Corporation.

We take this opportunity to thank the Medical and Research Directors of these firms.

†To be published later.

‡D-, Day since the onset of the experiment.

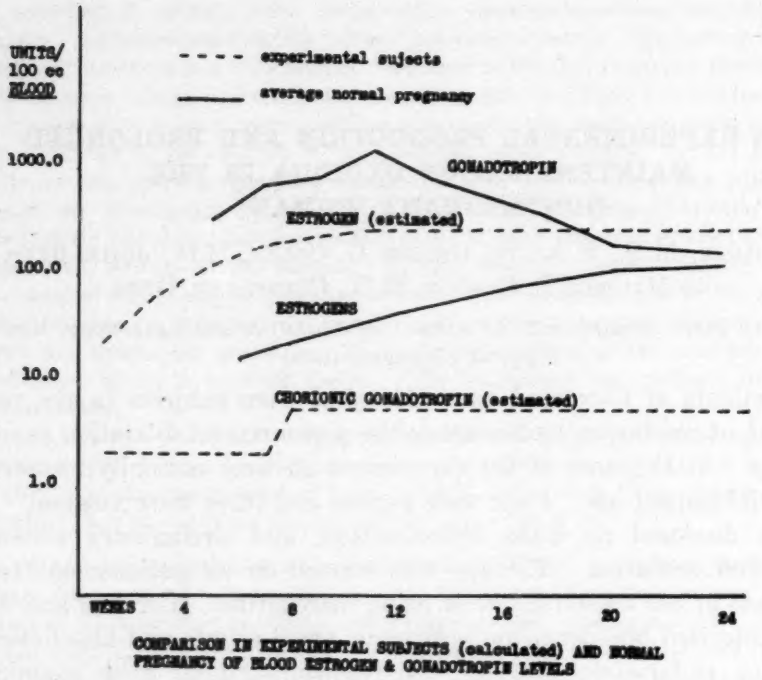
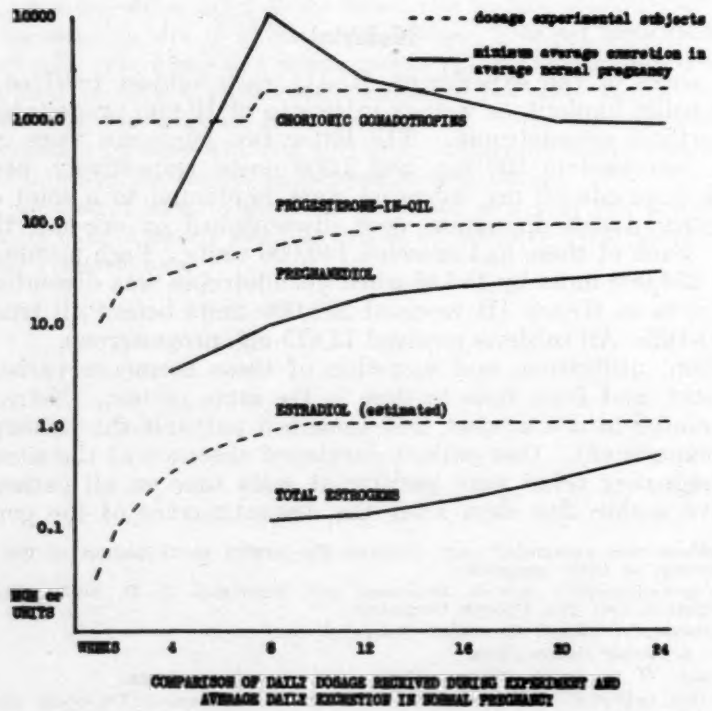

UNITS/
100 cc
BLOOD
experimental subjects
average normal pregnancy
1000.0
100.0
10.0
1.0
GONADOTROPIN
ESTROGEN (estimated)
ESTROGENS
CHORIONIC GONADOTROPIN (estimated)
WEEKS
4
8
12
16
20
24
COMPARISON IN EXPERIMENTAL SUBJECTS (calculated) AND NORMAL
PREGNANCY OF BLOOD ESTROGEN & GONADOTROPIN LEVELS

Fig. 1.


10000
1000.0
100.0
10.0
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RGH or
UNITS
dosage experimental subjects
minimum average excretion in
average normal pregnancy
CHORIONIC GONADOTROPINS
PROGESTERONE-IN-OIL
PREGNANEDIOL
ESTRADIOL (estimated)
TOTAL ESTROGENS
WEEKS
4
8
12
16
20
24
COMPARISON OF DAILY DOSAGE RECEIVED DURING EXPERIMENT AND
AVERAGE DAILY EXCRETION IN NORMAL PREGNANCY

Fig. 2.

Several had fully mature decidua in the presence of a negative test, whereas one patient on one occasion had "interval endometrium" with a positive test. After decidua was formed its maintenance in a mature state required all three hormones (Figs. 16 and 17).

Fig. 3.

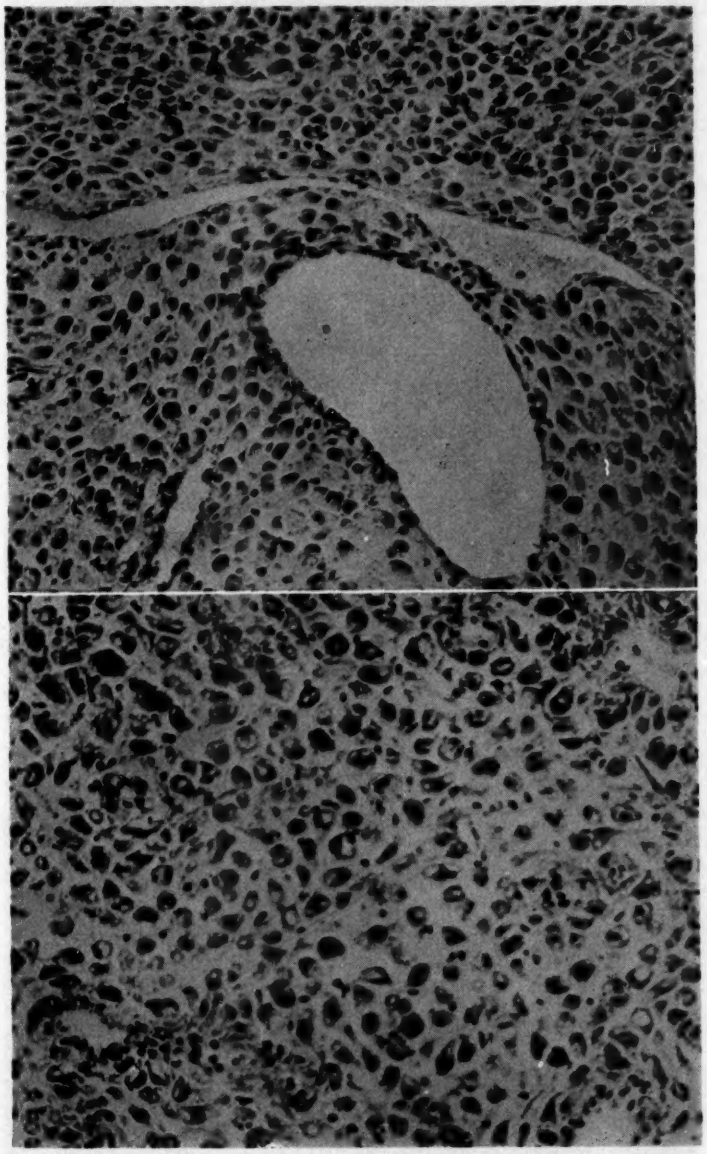

Fig. 4.

Fig. 3.—S.P. No. 64639. Glycogen deposits in normal decidua removed at therapeutic abortion in eight weeks' gestation. (Best's carmine.)

Fig. 4.—S.P. No. 64598. Glycogen deposits in experimental decidua on D-113. (Best's carmine.)

An attempt was made in these patients to produce and maintain a pseudopregnancy. We were unable to get sufficient amounts of chorionic gonadotropin, but using the figures of Perloff[8] for absorption of estradiol pellets, we calcu-

lated our dose so that serum levels would slightly exceed those found in normal pregnancy.[2, 9, 14, 15] Gray[3] states that he has been unable to confirm Perloff's work, but that the differences are probably due to different end points, Gray using mucification of the vaginal epithelium. He finds the daily absorption is

Fig. 5.

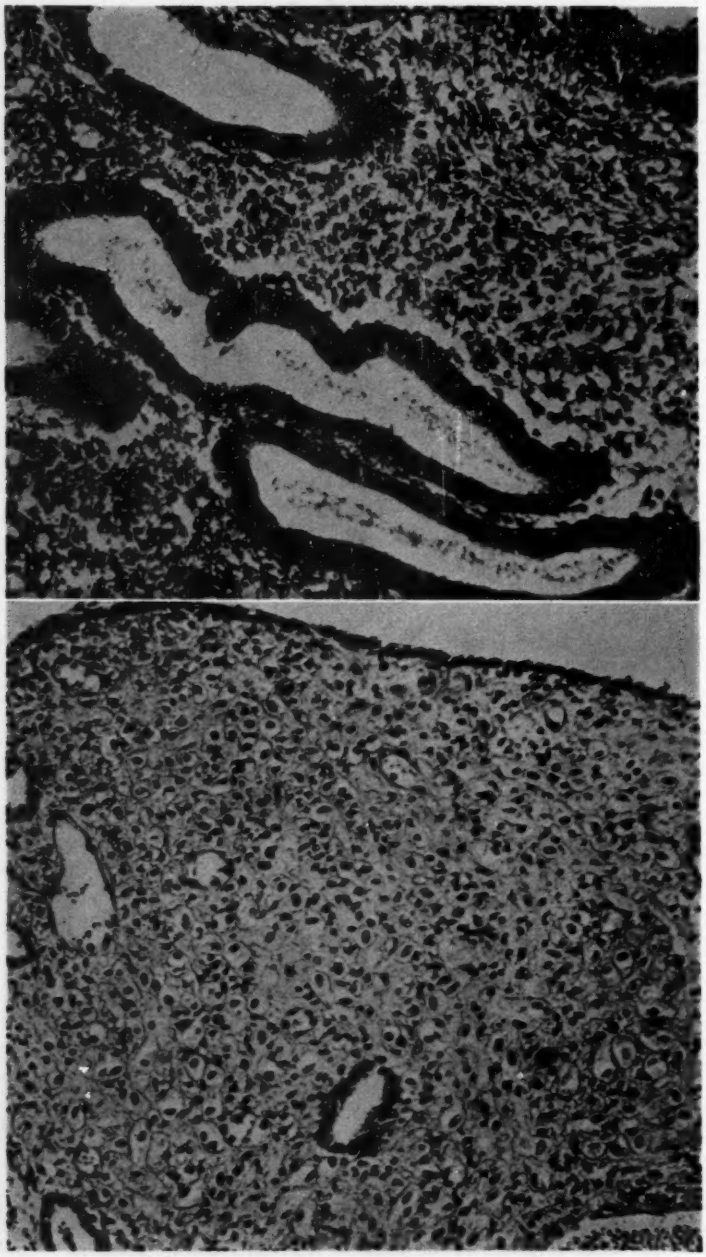

Fig. 6.

Fig. 5.—S.P. No. 63385. Midproliferative endometrium present at onset of experiment. (Hematoxylin and eosin.)

Fig. 6.—S.P. No. 63527. Typical decidua present on D-15 in same patient as in Fig. 5. (Hematoxylin and eosin.)

less, but that the duration of effect is much prolonged. Our calculated results are shown in Fig. 1. Fig. 2 demonstrates that except for chorionic gonadotropin, our dosage exceeds the minimal amounts excreted in the average pregnancy.[1, 4, 6, 11, 12, 13] We realize that new methods of isolating and identifying these hormones and their excretion products are constantly being developed and improved. However, in our present knowledge only 1 to 2 per cent of

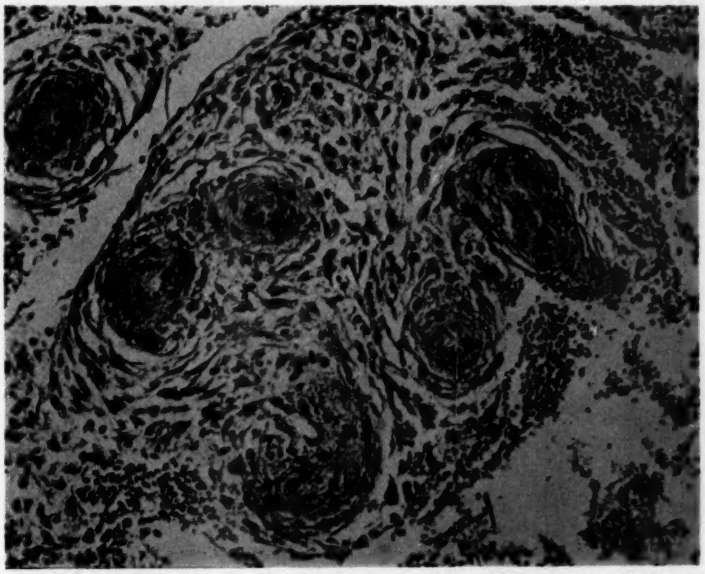

Fig. 7.—S.P. No. 63805. Spasm in spiral arteries. There is some edema of stroma. The glands are disintegrating but show residual evidence of secretion. (Hematoxylin and eosin.)

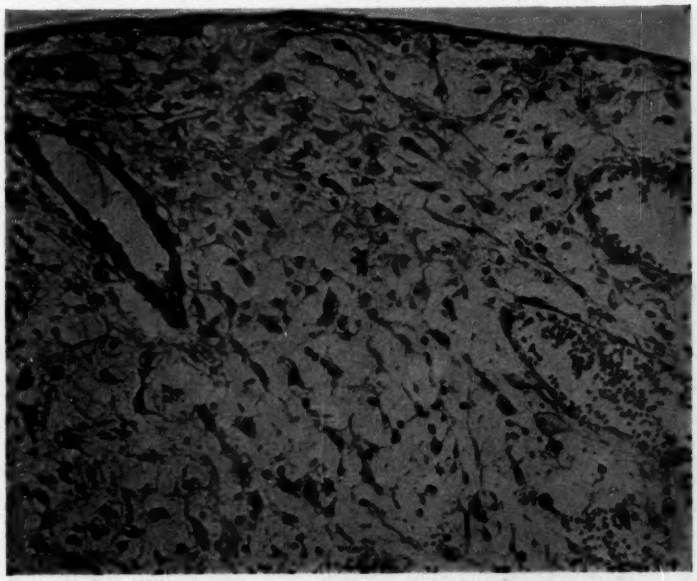

Fig. 8.—S.P. No. 64600. Marked edema and congestion with engorged and dilated capillaries. Glands lined by low cuboidal epithelium, and many of the nuclei lie parallel to the lumen. Surface epithelium is flat to cuboidal, and the nuclei lie horizontally. Stromal nuclei for the most part are small and oval and a few cells still contain cytoplasm. (Hematoxylin and eosin.)

formed estrogens are excreted, and urinary pregnandiol bears no definite relation to circulating progesterone.

Reynolds[10] states that glycogen disappears abruptly in the premenstrual endometrium, but persists under the influence of a corpus luteum in true decidua. Figs. 3 and 4 show the glycogen present in control decidua obtained at therapeutic abortion in an eight weeks' gestation as compared to that seen in the experimental decidua taken on D-113.

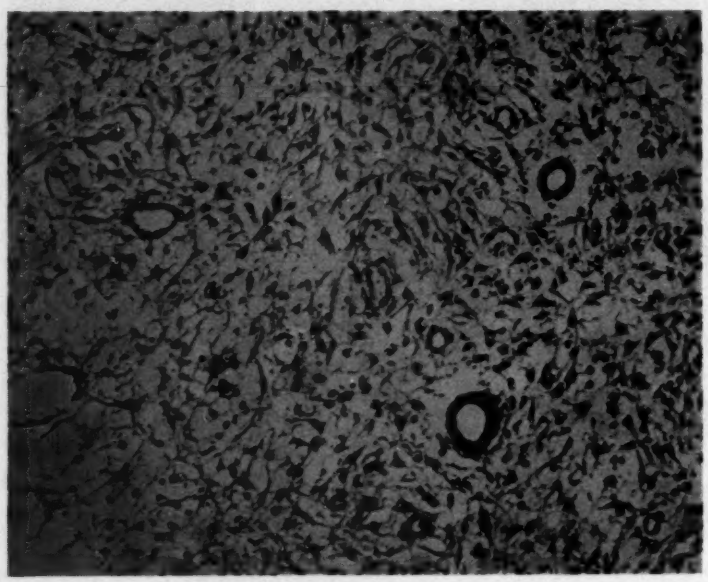

Fig. 9.—S.P. No. 64602. Active fibroblastic proliferation of the stroma. Mitoses are frequent. Edema is less than in preceding figure. Glands in stage of early active proliferation. (Hematoxylin and eosin.)

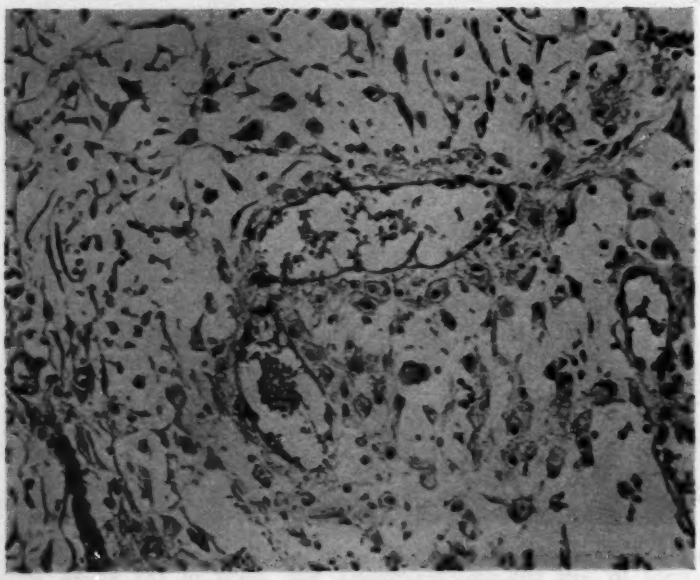

Fig. 10.—S.P. No. 64598. Earliest decidual reaction around capillaries. Discrete decidual cells in stroma with increasing cytoplasm and larger, less dense nuclei. (Hematoxylin and eosin.)

Figs. 5 and 6 show the biopsies on D-1 and D-15 on the same patient. They disclose mature decidua which developed within two weeks from interval endometrium dated, according to the criteria of Noyes, Hertig, and Rock,[7] as about the tenth day of a twenty-eight day cycle.

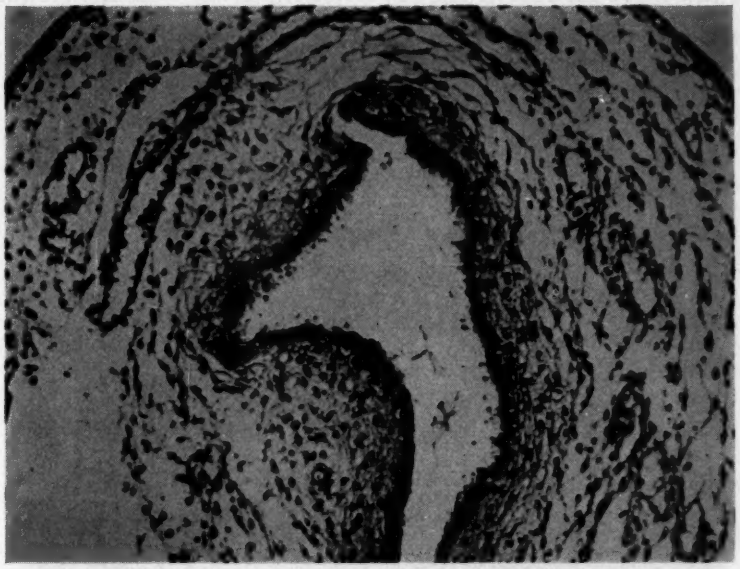

Fig. 11.—S.P. No. 64600. Slightly advanced stage of early decidual reaction with confluence of cells around gland. The gland is lined by a pseudostratified low columnar epithelium. The surface epithelium is low columnar with basal nuclei. The cells lining the glandular lumen are frayed at the edges and indistinct. (Hematoxylin and eosin.)

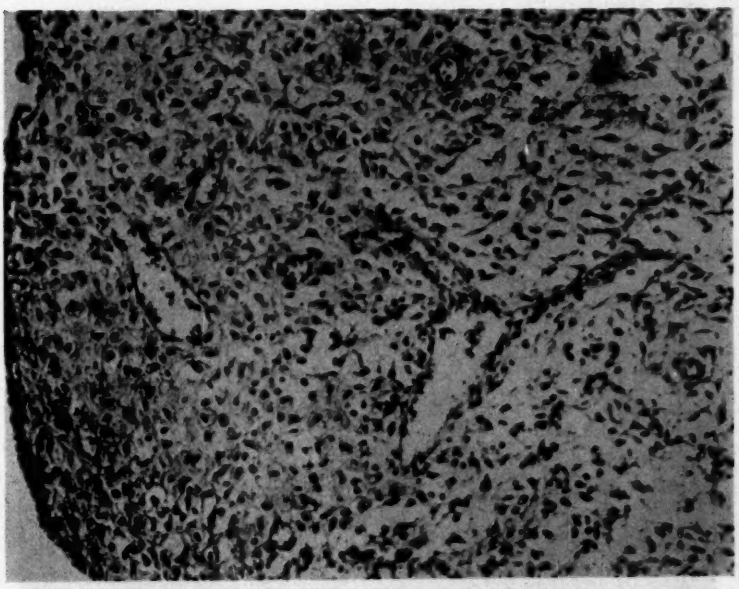

Fig. 12.—S.P. No. 63653. Decidual reaction under the surface epithelium (left border). This is a still later phase of development. The nuclei of the surface epithelium are again vertical to the tissue, though some cells are cuboidal with flattened nuclei. (Hematoxylin and eosin.)

Five of the eight subjects spotted on occasion during the first two months. Spotting varied from one to three days and was readily controlled by injections of stilbesterol, 5 to 25 mg. daily during the bleeding phase.

None spotted for more than a total of ten days, and spotting on no day approached that of even the last day of a normal period. There was no bleeding during the last three months of the experiment. Even with the frequent finding

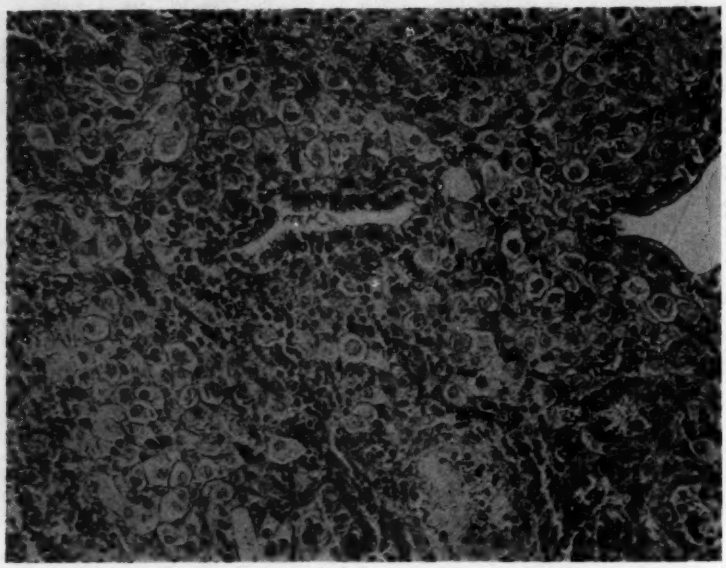

Fig. 13.—S.P. No. 63531. Coalescence of what appear to be mature decidual cells in stroma. These surround glands lined by low columnar epithelium. Gland edges are indistinct, the nuclei are vertical and in mid-position. Evidence of secretion is present within the gland lumen. There is a moderate infiltration of polymorphonuclear leucocytes at the left border. (Hematoxylin and eosin.)

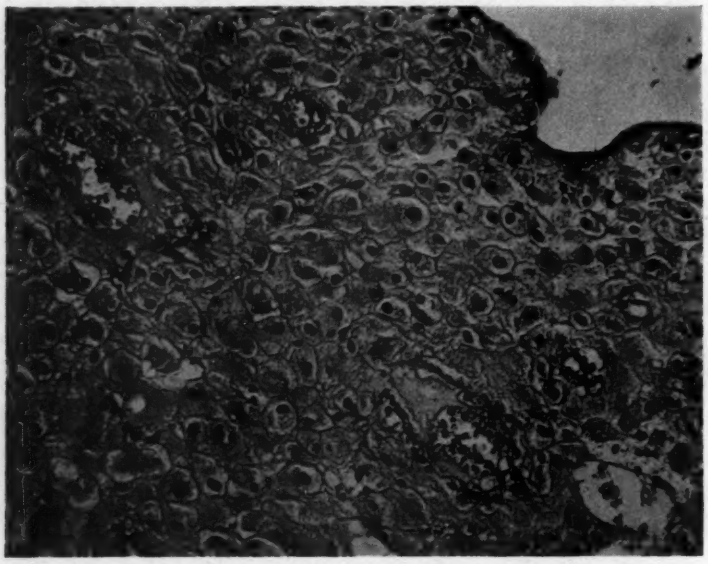

Fig. 14.—S.P. No. 63800. Mature decidua. The stromal cells are epithelioid and have a luminous collar. The nuclei are large, pale, and oval. (Hematoxylin and eosin.)

of "necrotic decidua," bleeding did not occur. Mature decidua was present as early as D-15. Necrotic and actively proliferating decidua were often found on adjacent sections of the same block. In the middle third of the experiment, it became increasingly difficult to obtain adequate biopsies in some of the patients, and approximately 15 per cent of the specimens were reported as "tissue

Fig. 15.—S.P. No. 64599. Inactive glands of the basal layer within the myometrium. (Hematoxylin and eosin.)

Fig. 16.—S.P. No. 64814. Endometrial response on D-134, 25 days after discontinuance of chorionic gonadotropin. Estradiol pellets active, and patient was receiving 100 mg. progesterone daily. (Hematoxylin and eosin.)

insufficient for diagnosis.'' The remainder were studied. These constitute the basis for this report. Figs. 7 through 14 were selected to show the steps in the transformation of endometrium to decidua. These disclose the changes which occurred in the surface epithelium, the glands and the stroma.

Mucosal swelling is noticed first. This is a continuation of that which originates in the normal secretory phase. Marked edema develops which separates the stroma from the glands and the glands from each other. The glands are compressed, and many disappear, some by visible fragmentation. The cell outlines of the glandular and surface epithelia become more indistinct, and, if disintegration is complete, the nuclei are the last to disappear. The cells which remain become cuboidal, then flattened. The nuclear axes change from the vertical and lie parallel to the glandular lumen or the tissue surface. Proliferation with glandular and surface regeneration follows and the cells again become cuboidal to low columnar, the nuclei round and surrounded by clear cytoplasm. Mitoses are frequent. The basal glands remain in the resting phase (Fig. 15).

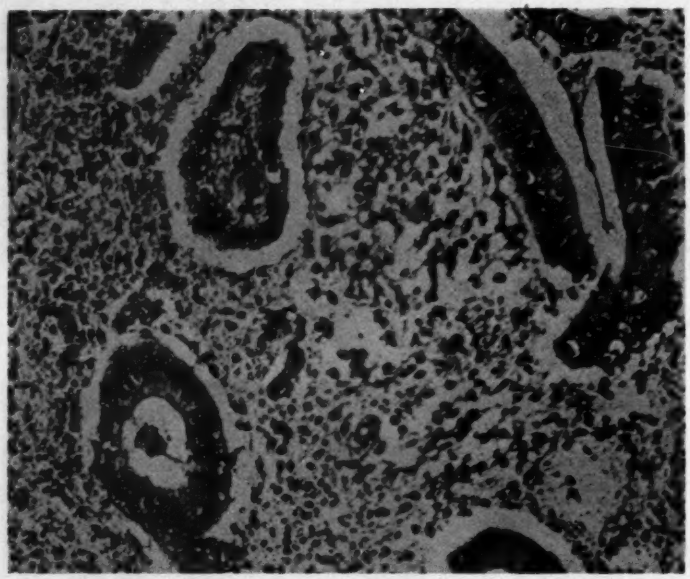

Fig. 17.—S.P. No. 65181. Endometrial response on D-162. Progesterone injections were stopped 10 days previously. Estradiol pellets active, and patient was receiving 2,000 units chorionic gonadotropin daily. This tissue varied from actively proliferating to typical "Swiss cheese" endometrium. Polypoid hyperplasia was present in some sections. (Hematoxylin and eosin.)

In the stage of edema there is marked spasm of the spiral arteries, succeeded by vascular dilatation, new capillary growth, and increasing congestion. Stromal proliferation begins and mitoses become increasingly numerous. The stromal cells become typical fibroblasts, stellate in shape. The cells gain cytoplasm and the nuclei become oval. More deep-staining cytoplasm is acquired and the nuclei are now larger and paler. The cells become polygonal and appear epithelioid. This occurs almost simultaneously around the glands, the capillaries, and under the surface epithelium. Discrete decidual cells appear in the stroma. These coalesce into small and then larger groups until mature decidua is formed. Surface epithelium is frequently absent at this time. Decidua is not a static tissue, but goes on to complete necrosis in some areas while

developing in adjacent sections. When chorionic gonadotropin or progesterone was discontinued, mature decidua remained for at least one week, but disappeared within four weeks.

Table I is a brief summary of the protocols of the eight subjects. All but one developed leucocytosis, and five had a rather marked eosinophilia. Two with eosinophilia also had a relative lymphocytosis. This suggests a possible reaction on the adrenals. This problem is now under investigation, and the patients will be followed until there is complete recovery.

TABLE I. COMPOSITE SUMMARY OF PATIENTS

Name	M.B.	M.D.	V.H.	M.Mi	M.Mt	R.M.*	S.S.	M.S.
Hospital number	34780	34687	34376	36467	36471	32617	36469	32827
Age (years)	35	35	40	31	35	41	30	33
Married	No	Yes	Yes	Yes	No	Yes	No	No
Parity	0	0	2	1	2	1	0	0
Grouping†	1	1	2	2	2	1	1	2
Total days spotting	10	0	3	3	1	1	0	0
Last spotting day	D-61	-	D-47	D-44	D-22	D-72	-	-
First decidua	D-15	D-29	D-29	D-15	D-15	D-43	D-29	D-15
"No diagnosis" reports	1	1	1	1	0	3	1	3
Hematology (all originally within average normal limits)								
RBC	3.91	4.20	5.04	4.40	5.20	3.57	4.03	4.48
HGB (Gm.)	12	12	14	12	15	10	12	13
(%)	78	78	91	78	98	65	78	85
WBC	15950	18400	15050	12350	11500	20200	7250	19200
% Polymorphonuclear leucocytes	77	75	75	59	56	82	66	64
Lymphocytes	17	16	24	34	31	16	16	26
Eosinophiles	-	5	1	6	5	-	14	5
Total eosin. count		920	150	740	575		1015	950

*Developed abscesses at sites of injection; estradiol pellets encapsulated.

†Group 1: Received chorionic gonadotropin and progesterone throughout experiment.
2: Progesterone as in Group 1; no chorionic gonadotropin last two months (after D-108).

Summary

Eight normally menstruating women of childbearing age at Cleveland State Hospital were subjects in the problem of producing by hormones the pyeloureteral dilatation common in pregnancy. Each received 275 mg. estradiol by pellet implant and 12,875 mg. progesterone by injection. Half received chorionic gonadotropin during the first two-thirds of the experiment only. The others received up to a total of 282,000 units. Endometrial biopsies done at intervals were studied and form the basis of this report on the experimental production and maintenance of decidua. The response persisted for over five months, and required all three hormones for its maintenance.

We sincerely appreciate the extensive cooperation offered us by Dr. E. H. Crawfis, Superintendent of Cleveland State Hospital, and his associates of the medical and nursing staffs. We are deeply indebted to Dr. B. S. Kline, Director of Laboratories at Mt. Sinai Hospital, and Dr. R. L. Faulkner, Assistant Professor of Gynecology at Western Reserve University School of Medicine, for their assistance in the interpretation of the specimens which were prepared by Miss Josephine Jones and photographed by Mr. William Stevenson of the Mt. Sinai Department of Laboratories.

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MYOMETRIUM AND LEIOMYOMAS IN ENDOMETRIAL CARCINOMA. FAILURE OF INVOLUTION AND REACTIVATION OF SMOOTH MUSCLE TISSUE

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THE problems dealt with in the forthcoming paper were first encountered when casual and subsequently systematic observations on uteri removed for endometrial carcinoma showed that on the average their size was considerably larger than normal for the age group of the patients. This was especially conspicuous in the late postmenopausal phase, in women past 60 years of age, in whom a small and atrophic organ, weighing not more than 30 to 50 grams was to be expected. Instead, often large specimens of two to three times normal weights and measurements were observed. The myometrium, rather than being thin, flabby, rubbery, of a dead grayish-pink, was thick, meaty, turgid, firm, of deep pink or rosy color. On the whole, these uteri looked "youthful," like premenopausal uteri.

Relation of Size of Carcinoma to That of the Whole Organ

Naturally the question arose whether this enlargement might not be substantially due to the mass of the tumor present in these uteri. Our observations did not bear this out; the hypertrophy was present with small, incipient carcinomas as well as with advanced ones and the size of the malignant tumor was not in proportional relation to that of the entire specimen. In a few instances relatively large carcinomas were found within small uteri and much more often small carcinomas in large uteri. The same quantitative relations held true for autopsy specimens of endometrial carcinoma.

The exact estimation of the relative mass of malignant tumor and surrounding myometrium is extremely difficult if not impossible. As far as possible, quantitative estimations of the relative mass of tumor and myometrium were taken; in infiltrative tumors, especially after radiation, the estimation had to rely upon impression. From our available data it appears that in the great majority of cases the mass of the carcinoma was below one-fifth of the total specimen, often between one-tenth and one-twentieth; in the irradiated uteri only microscopic traces of tumor of negligible mass were found. The conclusion of these quantitative findings was that the enlargement of the uterus was mainly due to hypertrophy of the myometrium.

Microscopic Studies of the Myometrium

The gross impression of hypertrophy of the myometrium found its counterpart in our microscopic studies of our material.

Muscle Fibers.—Normally, with the approach of the menopause, the muscle fibers of the myometrium start to shrink, becoming thinner with increasing quantities of collagenous fibers appearing between them. Still later they may lose their identity completely. Often a homogeneous mass of collagenous or hyaline fibrous tissue is all that is left between nuclei. In connective tissue stains this fibrous transformation of the aging uterus is clearly demonstrable.

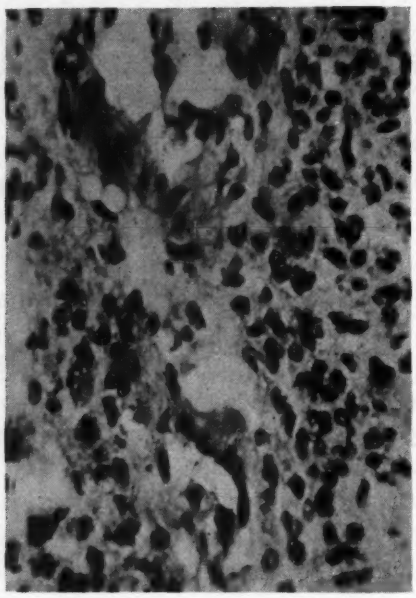

Fig. 1.—Senile myometrium, women 60 years old. No recognizable muscle fibers; pyknotic bean-shaped nuclei.

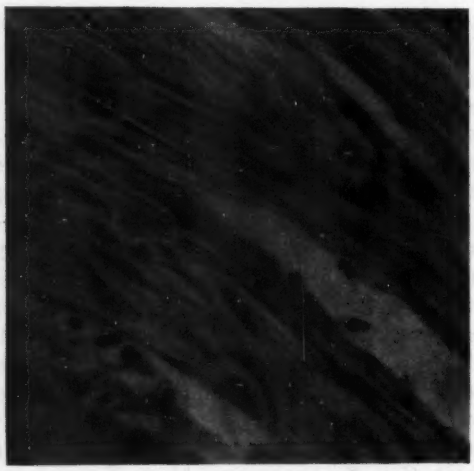

Fig. 2.—Endometrial carcinoma, woman 72 years old. Rejuvenation of myometrium; long muscle fibers.

In contradistinction, in the pertinent cases of our study, the muscle fibers were clearly identifiable, often long, broad, sometimes presenting a peculiarly luscious aspect, not unlike those of pregnancy. This reactivation or (in

younger patients, closer to the menopause) failure of involution was clearly distinguished from edematous changes. Where these occurred there resulted a sheetlike blurred picture of swollen collagenous fibers; small lacunae appeared in the hyaline or fibrillar ground substance. The nuclei present in these areas did not show the characteristic changes which will be described later on. In several cases of infiltration of the myometrium by carcinoma of the ovary and in one case by metastatic breast carcinoma there occurred no gross hypertrophy of the myometrium nor microscopic reactivation of the musculature.

Fig. 3.—Endometrial carcinoma, woman 59 years old. Rejuvenated myometrium; oval vesicular nuclei.

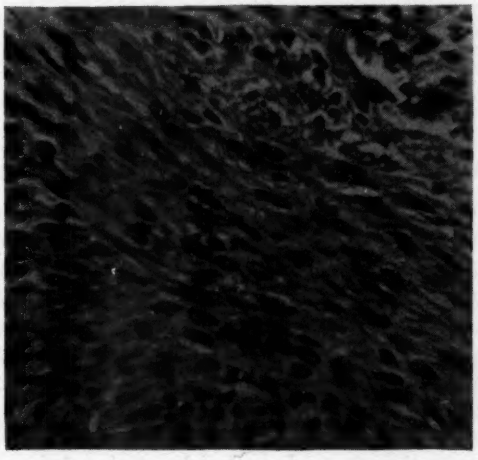

Fig. 4.—Myometrium of woman 69 years old. Rejuvenation through prolonged estrogen therapy.

Behavior of Nuclei.—The shape of the involuted myometrial nuclei is elongated, thin, rodlike, sometimes kinked, tortuous, and worm-like. On cross-section they are small, irregularly roundish, bean, or kidney shaped. They stain deeply, like pyknotic nuclei; the nuclear membrane is thick, the chromatin sometimes clumped. They are usually densely packed due to the lack of fibrillar substance. In the uteri with myometrial hypertrophy the nuclei become larger.

In the longitudinal sections they assume an oblong elliptic or even oval shape, losing their rod-like aspect; in cross sections they lose the indented kidney- or bean-shaped contour, becoming perfectly circular. They stain lighter with hematoxylin, the nuclear membrane is thinner. The entire nucleus shows the scanty, spotty chromatin distribution of vesicular nuclei.

Zonal Inequality of Changes.—A peculiar zonal inequality of these changes was sometimes noted. Conspicuously large muscle cells were found around the larger vessels in the periphery of the uterus. Farther inward there followed a zone of lesser cellular changes, of relative quiescence; finally, adjacent to the lumen and the cacinomatous areas there ensued a broad zone of very marked changes.

Cellular Changes in Grossly Not Enlarged Uteri.—Not all our specimens of carcinomatous uteri were grossly enlarged, approximately 35 per cent showing measurements and weights within the normal limit for the age group. However, even in these uteri, the above-described cellular changes were evident, sometimes in smaller or larger foci separated by quiescent areas. We gained the impression that the first changes in the process of reactivation involved the nuclei at a time when the muscle fibers were still quiescent and hardly identifiable.

Behavior of Blood Vessels.—Numerous new, small and large blood vessels were present all through the myometrium. This increase was noted in the myometrium adjacent to the carcinoma as well as in areas remote from its site.

Reaction of Reactivated Areas With Special Stains.—While most of our cases were studied with routine hematoxylin-eosin stains, Mallory-Azan and van Gieson stains were also used in a number of selected cases. With both these stains the impression of reactivation of the muscle fibers gained in the routine hematoxylin-eosin preparations was confirmed.

Definition of "Rejuvenation."—The macroscopic and microscopic changes described above resulted in a picture resembling the premenopausal myometrium. Since these changes were most conspicuous in late postmenopausal cases the term "rejuvenation" was considered most adequate for a comprehensive definition of the entire complex; it will be subsequently used.

Influence of Radiation on the Size of Uteri and Myometrial Changes

The most commonly used procedure in treating endometrial carcinoma at present is the intrauterine application of radium, followed after 6 to 8 weeks by total hysterectomy. According to the clinical impression of the gynecologists, the radium treatment is accompanied by a very marked shrinkage of the uterus, sometimes down to one-half or even less of its original size. In the cases where measurements of the uterine lumen prior to administration of radium were taken, an approximate shrinkage of one-third was noted at the subsequent hysterectomy. These studies are continued at present. How much of this shrinkage is due to regression of the tumor and how much to that of the myometrium is difficult to estimate and probably varies from case to case.

This impression is corroborated by the microscopic findings in irradiated and nonirradiated uteri. Whereas edema and necrosis of the parts of the myometrium adjacent to the lumen are common, these changes are totally different from the rejuvenation reaction. In fact, the most characteristic and clear-cut myometrial rejuvenation was observed in nonirradiated uteri. The spotty and focal distribution of rejuvenated areas mentioned above was most often found in irradiated uteri, perhaps a regression of the previously reactivated tissue toward the involutional stage due to the radiation effect.

Leiomyomas Present in Carcinomatous Uteri

Our studies revealed that leiomyomas present in the carcinomatous uteri frequently participated in the process of rejuvenation.

The natural history of the leiomyoma calls for involution at the menopause, similarly to the myometrium. Even before that time their tendency to undergo hyaline and fibrotic changes often inhibits their further growth. The normal aspect of postmenopausal myomas is that of quiescence; they look grossly and microscopically "dead," even more so than the myometrium. Their cut surface is smooth. As a rule they are of leathery, sometimes extremely hard, dry consistency; their color is whitish gray. Hyalinization and more or less extensive calcification are common. Their size is of course dependent upon what it was before the menopause, for example, a grapefruit-sized tumor may shrink to the size of a peach and a peach-sized one to that of a cherry. Microscopically, the same changes as described for the involutional myometrium take place. The cells become small and often scarce, the muscle fibers disappear. Large areas of acellular hyalinization are present; vessels are calcified and often occluded, small vessels and capillaries are extremely scanty.

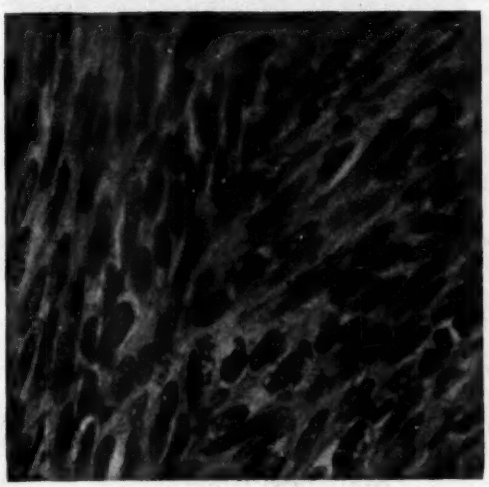

Fig. 5.—Cellular, active leiomyoma in woman 58 years old with endometrial carcinoma.

The majority of the leiomyomas associated with endometrial carcinomas presented an entirely different picture. In the gross aspect they showed the whorly uneven cut surface of the premenopausal tumors; they were of elastic, resilient, or turgid, sometimes even succulent or edematous, consistency; their color was pinkish in varying shades of depth. As a group they were considerably larger than those found in nonmalignant uteri; they impressed one as actively growing. The microscopic picture corresponded to the gross impression. Some of these leiomyomas were very cellular, even resembling a low-grade sarcoma; their muscle fibers were comparatively small, the nuclei large and vesicular, mitoses were increased in numbers. The leiomyomas of this type were evidently of recent origin, not reactivated dormant tumors. In this latter type there prevailed a different process. Islands of actively growing muscle cells with long fibers and oval thin-walled nuclei alternated with dormant areas of acellular hyaline tissue. In other areas single young cells with large hyperchromatic nuclei developed within the hyaline tissue, there were also numerous newly formed capillaries lined with cuboidal endothelia. In still other areas of

previous homogeneous hyalinization an over-all breakup of these hyaline masses by diffusely proliferating muscle cells was observed. These cells were usually seen in small groups, surrounded by lacunary spaces. The still remaining hyaline tissue formed a peculiar reticulated pattern between these rejuvenated cell groups. Calcifications in these myomas show marginal resorption of calcific granules; there was apposition of macrophages at the decalcified fringes; new blood vessels were observed in their immediate neighborhood, old occluded ones were undergoing recanalization.

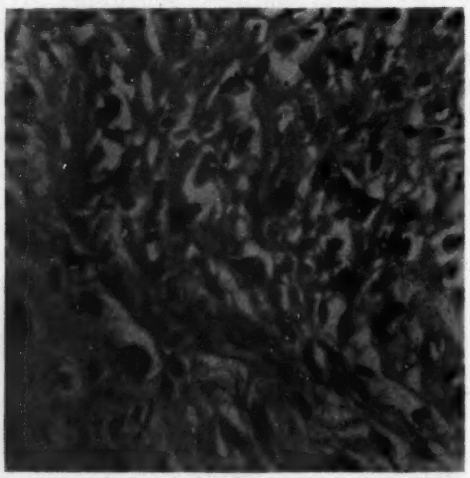

Fig. 6.—Woman 80 years old, endometrial carcinoma. Focus of reactivation in leiomyoma; reticular pattern; massing of nuclei, large phagocytes.

Large cells, with deeply eosinophilic or basophilic cytoplasm and oval nucleus were found in great numbers in and around the lacunary spaces of the rejuvenated myomas. Some of them showed small dark-stained cytoplasmic inclusions. In all probability these cells are specialized macrophages, with the task of removal of the hyaline matter.

Statistical Observations

The statistical work-up was undertaken on a material of 1,153 uteri, removed during the past 5 years. There were 1,095 nonmalignant and 58 malignant cases. Twelve additional uteri with carcinoma were used only in the first part of the statistical considerations (see below), on account of insufficient measurements. These considerations divided themselves naturally into two groups:

Group I. The percentage of uteri with endometrial carcinoma in which the above-described macroscopic and microscopic changes of the myometrial elements were present.

Group II. A comparison of weights and measurements between the malignant and nonmalignant groups of uteri.

Group I. Percentage of Carcinomatous Uteri With Rejuvenation of the Myometrium

The statistical work-up of this group encountered considerable difficulties. Endometrial carcinoma is usually a disease of the menopausal and postmenopausal age group; a certain precentage of cases will occur before the clinically

recognizable menopause. In these latter cases and also in the cases occurring during a transitional period which arbitrarily was set at between 50 and 60 years of age histologically active myometrium may be a normal finding or simply a retardation of the involution as it may occasionally occur, especially in the present age of widely used estrogen therapy. It may however be stressed that in all of them myometrium of premenopausal type was present, whereas in the nonmalignant uteri of the age group between 50 and 60 years only 23 per cent showed premenopausal type myometrium.

There remained a group of 14 carcinomatous uteri of women past the age of 60 years. Of these, one with a minute carcinoma which was incidentally detected (the uterus was vaginally removed for prolapse) showed no rejuvenation changes; all the others, 93 per cent of this small series, showed various degrees of rejuvenation. Although this group is small, its high percentage of myometrial reactivation fits in with the impression we gained from the studies of the whole malignant group.

Group II. The Comparison of the Weights and Measurements Between the Malignant and the Nonmalignant Groups

This could be undertaken only after previous analytical considerations of all the factors influencing the weight and size of the removed uteri. The first consideration was given to different age brackets. The greatest difference in weights was to be expected in the late age group when the normal uterus should be small and atrophic. On the other hand, in the premenopausal age group this difference should be relatively small since the nonmalignant specimens of this group would normally be relatively big, their myometrium still active, and enlargement due to myometrial changes in the carcinomatous specimens could be only of minor nature. For these reasons it was thought best to establish four age brackets, a predominantly premenopausal bracket before the age of 50, an early and late transitional bracket between the ages of 50 and 55 years and 55 and 60 years, respectively; a late postmenopausal group of over 60 years.

These expectations are borne out by our figures. The smallest percentage-wise difference is present in the youngest age group, the highest in the oldest one, increasing through the transitional groups (Table I).

There are some more factors which should be considered with these statistics and which have the effect of intensifying this trend of increasing spread of weight and measurements with higher age.

In the nonmalignant group below 50 years of age, there were a large number of partial hysterectomies, in which the cervix was left in the body. The weight of the cervix in this age group is not inconsiderable, varying between 10 and 30 grams. If this weight were added to the weight of the removed corpus, it would produce a corresponding statistical increase in the weight of the specimens of this group. On the other hand, the malignant uteri of this age group, as well as those of the other age groups, are removed by total hysterectomy, the weight of the cervix already implied in their total weight. Thus, the divergency in weights in the premenopausal age group is in reality slightly smaller than expressed in our statistics.

In the late postmenopausal age group this difference between the weights of the nonleiomyomatous malignant and nonmalignant uteri is in reality greater than apparent from our figures if we consider the fact that most, if not all of these nonmalignant uteri have been removed for prolapse. Due to the elongation of the cervix, these uteri are mostly long and thin; the largest specimen

of this group for instance weighed 105 grams and measured 12 by 3 by 2½ cm. In our experience approximately one-third to one-half of the weight of these prolapsed uteri is the weight of the cervix. Nonprolapsed uteri of this age group with their extremely small cervices, as for instance those incidentally removed at autopsies, weigh rarely more than 30 grams. Therefore, the real weight of these uteri without the enlarged cervix would be smaller and the percentual increase of the malignant over the nonmalignant group would be higher than our figures indicate.

TABLE I

	NO MALIGNANCY NO LEIOMYOMA	MALIGNANCY NO LEIOMYOMA	NO MALIGNANCY LEIOMYOMA	MALIGNANCY LEIOMYOMA
Age Group Under 50 Years.—				
Number of cases	327	12	533	16
Average weight	124 Gm.	12 Gm.	320 Gm.	420 Gm.
Weight range				
Low	20 Gm.	80 Gm.	20 Gm.	60 Gm.
High	220 Gm.	320 Gm.	1460 Gm.	1220 Gm.
Weight increase of malignant group	44%		31%	
Age Group 50-55 Years.—				
Number of cases	43	4	88	4
Average weight	107 Gm.	145 Gm.	275 Gm.	467 Gm.
Weight range				
Low	20 Gm.	80 Gm.	20 Gm.	60 Gm.
High	220 Gm.	320 Gm.	1460 Gm.	1220 Gm.
Weight increase of malignant group	31%		70%	
Age Group 55-60 Years.—				
Number of cases	22	6	23	7
Average weight	90 Gm.	99 Gm.	140 Gm.	208 Gm.
Weight range				
Low	30 Gm.	60 Gm.	30 Gm.	80 Gm.
High	240 Gm.	180 Gm.	480 Gm.	460 Gm.
Weight increase of malignant group	64%		73%	
Age Group Over 60 Years.—				
Number of cases	34	6	25	3
Average weight	55 Gm.	90 Gm.	260 Gm.	450 Gm.
Weight range				
Low	20 Gm.	60 Gm.	40 Gm.	80 Gm.
High	120 Gm.	160 Gm.	200 Gm.	1100 Gm.
Weight increase of malignant group	64%		73%	

As stated before, it follows from our graphs and from the considerations of these factors in the youngest and on the other hand in the oldest age group that the higher the age, the greater the percentual weight increase of the malignant over the nonmalignant uterus. Besides the data presented in Table I we also charted incidence of adenomyosis and previous radiation. These additional data helped in analyzing cases, which appeared to fall out of the normal for their age-weight group; i.e. the surprisingly high weight of 140 grams in a noncancerous uterus of a woman 60 years old was explained by the presence of a large area of regressing adenomyosis.

Remarks Concerning the Individual Groups

We realize that the case number of our malignant material is too small to allow too close a statistical breakdown. It should however be of some significance that not only is the average weight of the malignant groups higher than that of the nonmalignant ones, but that throughout all charts the weight of the smallest malignant specimen is greater than the weight of the corresponding nonmalignant one and that the same is true of the largest specimens of each group.

Another clinically important conclusion of our figures is that in the age group above 60 years, if specimens with leiomyomas, adenomyosis, and prolapse are discounted, all uteri over 60 to 70 grams of weight show malignancy.

Findings in Sarcomas

The same changes as with carcinomas were in evidence in the myometrium of uteri with leiomyosarcoma. Furthermore, in the few cases observed in the late postmenopausal stage, marked endometrial hyperplasia accompanied the sarcomatous myometrial changes.

References in the Literature

As far as a careful study of the pertinent literature of the last 15 years and examination of older textbooks on pathology and gynecology could reveal, the complex of the present investigation has not been systematically covered before. Actually, the only reference which could be found at all is a short remark of Robert Meyer[1] in Henke-Lubarsch's *Handbook of Pathology*, citing Theilhaber and Hollinger,[2] "that sometimes hypertrophy of the myometrium accompanies endometrial carcinoma, mostly as independent myohyperplasia, not as a consequence of work-hypertrophy."

In the numerous papers on carcinoma and leiomyoma no systematic correlation of the size of the uterus and that of the myomas was made nor was their histology a subject of investigation except for the paper of Tibirica[3] describing the co-existence of a malignant fibromyoma and of adenocarcinoma of the uterus.

Pathogenetic Correlations

The findings of our study on myometrial reactivation and hypertrophy accompanying endometrial carcinoma appear to contribute more support to the theory of hormonal causation of endometrial carcinomas. We find in our own material actual proof that estrogenic hormones may affect both myometrium and endometrium. The histology of several uteri removed following energetic estrogenic therapy shows that both myometrium and endometrium react, the myometrium with rejuvenation, the endometrium with hyperplasia. The same concomitant reaction of both endometrium and myometrium was observed in two cases of thecoma of the ovary, one of which showed fully developed carcinoma, the other one massive adenomatous hyperplasia of the endometrium. In another case of carcinoma of the endometrium accompanied by marked myometrial rejuvenation, peculiar adrenal-like cell masses were found in the hilus region of the ovary.

The role of estrogenic hormones in proliferative processes of the postmenopausal endometrium has been well established by the reports of endometrial hyperplasia and even carcinoma following estrogen therapy, on the one hand, and endometrial carcinoma accompanying theca cell tumors, on the other hand.[5, 6, 7, 8, 9] While Novak[4] and Zondek[10] both believe that there is no conclusive evidence of uterine cancer caused by estrogen therapy, there are re-

ports by Vass[13] and M. Fremont Smith and associates[14] of carcinoma of the endometrium following this type of therapy. Herrel[12] has never seen carcinoma of the endometrium after oophorectomy in 241 cases.

While thus there is on the whole a mounting amount of indication of the role of endocrine factors, especially of ovarian origin in the causation of endometrial benign and malignant proliferative processes, the question arises where the production of these hormones takes place in the postmenopausal ovaries without thecoma or granulosa-cell tumors. Shaw and associates[15] found peculiar endocrinoid cells in the ovarian hilum in 24 out of 48 cases of endometrial adenocarcinoma. They hold that these cells probably originate from the endothelium of small capillaries or lymphatics since they were invariably found in the neighborhood of blood vessels. They denied the possibilities that their cells are identical with the hilum cells which are described in the paper of Sternberg.[16]

The structure of the ovarian stroma itself long considered as consisting of connective tissue-like elements has lately been the subject of several studies resulting in a substantial revision of this interpretation. Novak[4] points to the possible influence of stromal hyperplasia on the spontaneous postmenopausal hyperplasia. Schwarz and Young,[17] in a paper dealing with the histology and development of the ovarian stroma, are of the opinion that the cells of the ovarian stroma are derived from the vascular walls and, judging from their morphologic and staining characteristics, show much more the properties of smooth muscle than of connective tissue. DeGiorgi[18] stresses the structural similarity of the ovarian stroma to erectile tissue. Woll and associates[19] found stromal hyperplasia of the ovary in 56 to 92 per cent of cases of carcinoma of the uterus, whereas in control groups this hyperplasia was present in 36 to 42 per cent.

In a preliminary survey of the ovaries removed together with carcinomatous uteri we too gained the impression that the degree of stromal hyperplasia was larger than in the control cases. However, this impression needs further systematic studies corroborated by connective tissue and fat stains for future evaluation.

Clinical Significance

Aside from the theoretical aspect of the problem, its practical clinical side should also be stressed. A nonprolapsed uterus of the late postmenopausal age group which is distinctly larger than normal should by its size alone arouse suspicion of intrinsic malignancy or else of a hormone-producing ovarian tumor. The same is true of myomas which show signs of reactivation such as growth, pain, or soft, meaty consistency on palpation. It seems possible that increased clinical consciousness of these factors may in suitable cases lead to the diagnosis of malignancy in earlier and more favorable stages.

Summary

Gross and histologic studies on 58 uteri with endometrial carcinoma showed in a great percentage of cases failure of involution or reactivation of the myometrium (rejuvenation).

Leiomyomas present in uteri with endometrial carcinomas showed similar changes, leading to enlargement and reactivation of formerly dormant tumors.

Statistical comparison of malignant and nonmalignant uteri demonstrated higher weights in the former group, the weight difference percentagewise increasing with age.

The pathogenetic significance of these findings is discussed and correlated with findings of the literature and of our own observations supporting the view of a hormonal impact hitting the uterus in its totality, sometimes leading only to late endometrial hyperplasia, in other cases to carcinoma or sarcoma accompanied by myometrial hyperplasia.

The significance of these studies for a possible earlier clinical recognition of endometrial carcinoma is stressed.

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CONING BIOPSY IN THE DETECTION OF EARLY CANCER OF THE CERVIX*†

A Survey of 500 Normal Women

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(From the Department of Obstetrics and Gynecology of Columbia University and the Sloane Hospital for Women)

THE study and definition of the intraepithelial carcinoma of the cervix and the development of vaginal cytology according to the techniques of Papanicolaou have fostered a developmental concept of cervical cancer which may enable us to control this disease before we learn its cause or ideal treatment. There is no doubt that the stimulus in recent years for early detection has changed the problem of cervical cancer strikingly so that we may now expect to make the diagnosis of cervical cancer at a curable stage in the overwhelming majority of cases, with diagnostic methods existing at the present time.

With the accumulation of knowledge concerning intraepithelial carcinoma of the cervix, we have learned the importance of the region of the histologic external os as the trigger site of most of these early lesions. Biopsy of the squamous-columnar junction must be considered vital therefore to early detection. Papanicolaou type cell studies of cervical smears have helped us greatly in bringing some of these early cases under surveillance, and therefore they have frequently placed us in the position of responsibility for a relatively young woman with a cervix which is normal or clinically benign to examination with suspicious or frankly positive smears. We must not proceed to therapy without obtaining tissue for histologic examination by biopsy for the cytologic method is not absolutely precise, nor does it tell us the exact histologic nature of the lesion or its geographic limits. With the increased appreciation of the value of frequent and careful cervical biopsy has come a clinical realization of the inadequacy of punch biopsy techniques for securing a general sample from the relatively normal-appearing cervix. This deficiency has been met in some clinics by taking multiple samples from each cervix.[1, 2] We have not found the conventional punch biopsy instruments satisfactory for obtaining a suitable sample in this type of patient. Nor have the cervical scrapers or scalpels[3, 4, 5, 6, 9] appeared adequate for this use in that they seem to obtain a sample which lies midway between smear and biopsy; we have found an anesthetic necessary to obtain a proper segment for histologic study by these methods.

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†This study was supported in part by a grant from the New York City Cancer Committee.

We have answered this problem of taking a circumferential sample from the squamous-columnar junction of the relatively normal cervix without a well-defined lesion by the use of the endocervical coning biopsy curette.[7] This instrument enables us to secure a cone of tissue from the external os of the cervix in simple fashion, without an anesthetic, as an outpatient procedure. It has furnished us with a sound method for further documenting the vaginal smear and also with another type of screening procedure.

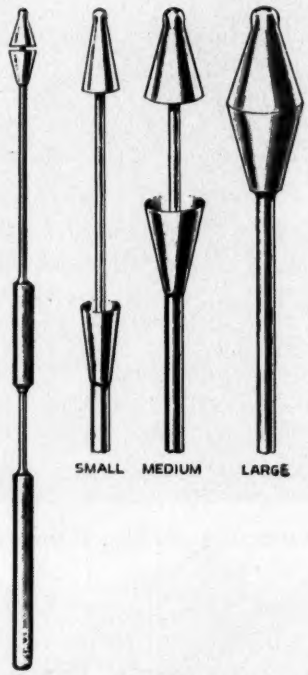

Fig. 1.

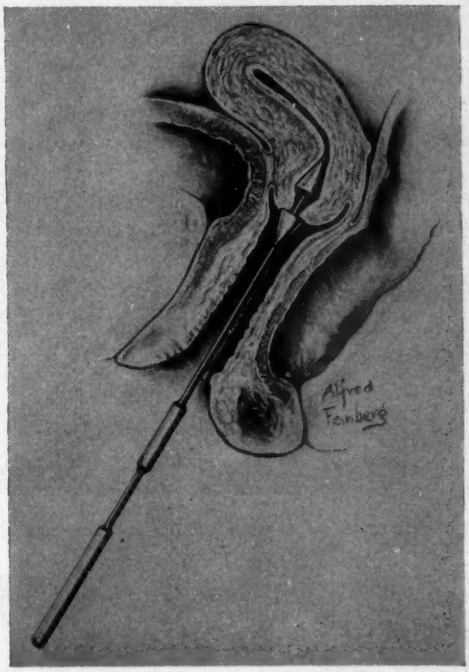

Fig. 2.

Fig. 1.—Endocervical biopsy curettes. Note open and closed positions of cutting cups.
Fig. 2.—Curette in cervical canal. The coning biopsy will remove the squamous-columnar junction region at the histologic external os.

Plan of Study

We have set up a detection group to make a survey of women over the age of 35 years without symptoms of uterine cancer. These patients have been selected from the general hospital diagnostic clinic by exclusion of those with any aberration of menstruation or history of abnormal uterine bleeding; we have also required that the pelvic examination of those selected should be free of any lesion considered suspicious of cancer. In such an age group, of course, one will encounter an occasional patient with asymptomatic fibroids or an innocent-appearing cervical erosion. We saw no reason to exclude such patients from a cancer detection survey, for it was our intent to ascertain the number of malignancies we could disclose in women who presented no clinical reason for taking such cancer diagnostic measures. Our study group also included a small number of asymptomatic private patients who had sought gynecologic consultation for simple periodic examination.

This report covers the first 500 patients in our study. Each of these patients in addition to pelvic examination was studied by vaginal and cervical cytologic smears and endocervical coning biopsy.

Technique of Biopsy

The instrument which we use to secure a circumferential coning biopsy from the squamous-columnar junction region was designed to supply our need

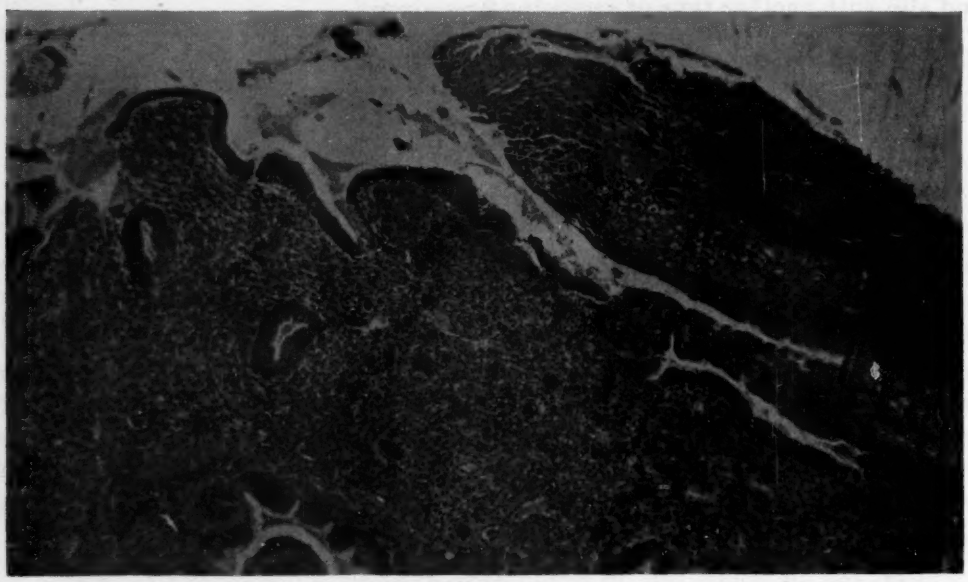

Fig. 3.—Normal squamous-columnar junction. Mild inflammatory reaction is present.

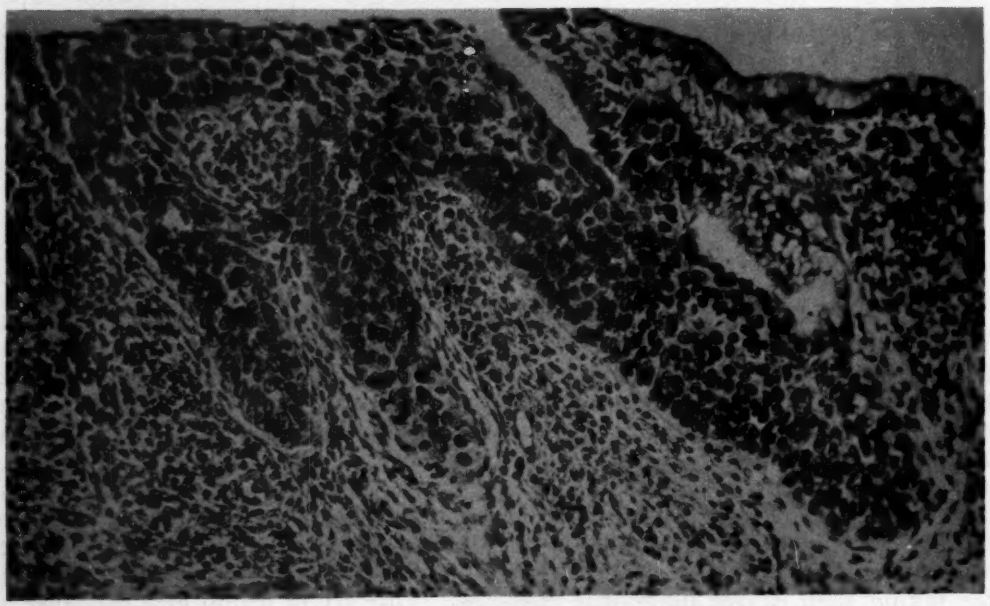

Fig. 4.—Intraepithelial carcinoma of the cervix. The malignant change is in the canal and dips down into glands. In other areas it has started to break through the basement membrane

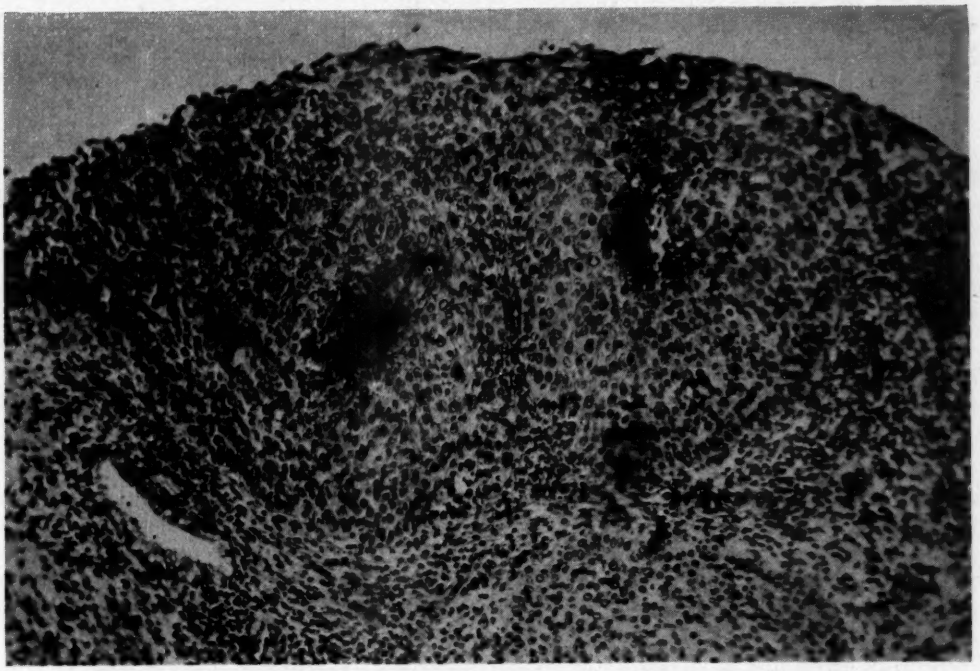

Fig. 5.—Intraepithelial carcinoma of the cervix with local areas of early invasion.

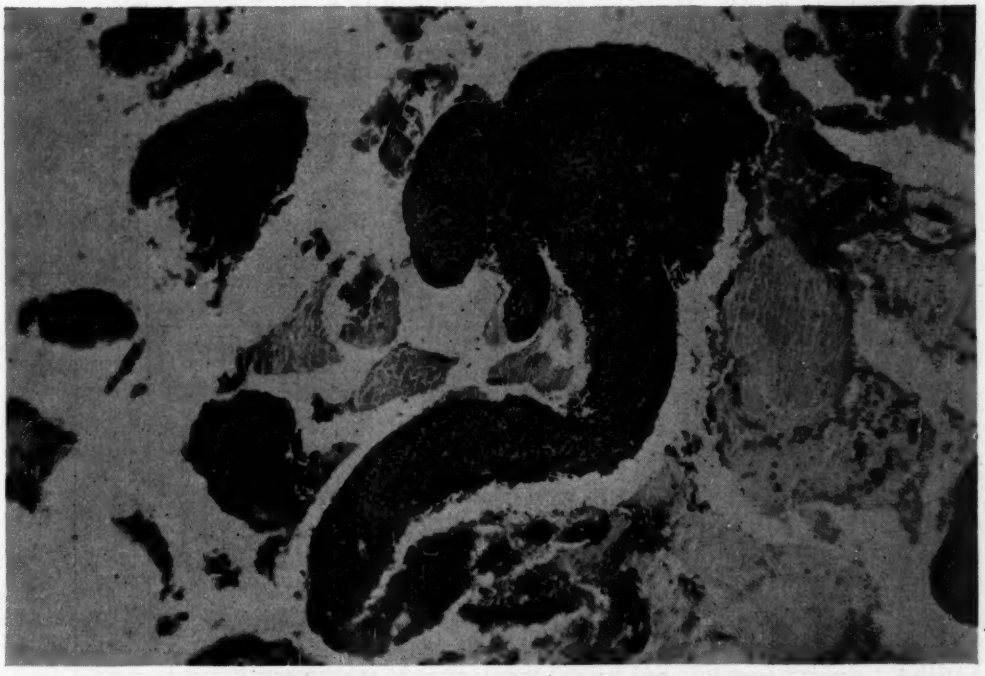

Fig. 6.—Intraepithelial carcinoma of cervix. It is interesting to note how frequently such surface lesions strip away from underlying stroma.

TABLE I. ENDOCERVICAL CONING BIOPSY. TOTAL GROUP SCREENED, 500 PATIENTS. ASYMPTOMATIC INTRAEPITHELIAL CARCINOMA OF CERVIX DETECTED IN 10, OR 2 PER CENT

	AGE (YEARS)	SYMPTOMS		DIAGNOSIS		ENDOCERVICAL CONING BIOPSY	SMEAR
		GENERAL	PELVIC	GENERAL	PELVIC		
C. P.	37	Abdominal and leg pain	Dysmenorrhea	0	Fibromyomata uteri Cervical erosion	Ca. of cervix, intraepithelial and early invasion (Fig. 4)	IV
I. G.	38	Lump in groin	0	Femoral hernia	0	Ca. of cervix, intraepithelial and early invasion (Fig. 5)	IV
B. H.	58	0	0	0	Chronic cervicitis	Intraepithelial ca. of cervix (Fig. 6)	V
A. S.	65	Rectal pain	0	Conversion hysteria	0	Ca. of cervix, intraepithelial and early invasion (Fig. 7)	IV
C. A.	34	RLQ pain	RLQ pain	0	Fibromyomata uteri Chronic salpingitis Chronic cervicitis	Intraepithelial ca. of cervix (Fig. 8)	V
V. B.	39	0	Abdominal pain	0	Chronic salpingitis Cervical erosion	Intraepithelial ca. of cervix (Fig. 9)	IV
M. A.	41	Anginal pain	0	Congenital heart disease	Cervical erosion No gynecological disease	Ca. of cervix, intraepithelial and early invasion (Fig. 10)	V
J. B.	36	Choking sensation in throat	0	Hysteria Possible duodenal ulcer	Cervical erosion No gynecological disease	Intraepithelial ca. of cervix (Fig. 11)	II
R. C.	41	Palpitation Lump in neck	0	Toxic goiter	No gynecological disease	Ca. of cervix, intraepithelial with early invasion (Fig. 12)	IV
T. H.	46	Pain left wrist	Stress incontinence of urine	0	Cystocele Rectocele Normal cervix	Intraepithelial ca. of cervix (Fig. 13)	V

for a technique which could be simply and safely applied to ambulatory patients, without need for anesthesia or special hemostatic measures (Fig. 1). As has been stated above, this biopsy technique was developed under the following concepts of cervical cancer detection:

A. Intraepithelial cancer can be found in a significant percentage of apparently normal cervices.

B. The squamous-columnar junction region is the most common site for the early development of such lesions.

C. The Papanicolaou smear is an excellent means of screening such apparently normal women, but it requires tissue confirmation; we know it is not absolutely precise, does not define the site or extent of the lesion, and requires skill and refinement of interpretation not at present available to the vast majority of pathology laboratories.

D. Punch biopsy techniques are inadequate for the normal appearing cervix; coning biopsy with the scalpel requires anesthesia, thus introducing a factor of complexity which limits the scope of screening.

The technique of biopsy with the endocervical coning biopsy curette has been described elsewhere[7] but it may be useful to review it briefly here. A curette is chosen of a size which fits the cervical canal snugly and it is introduced in the open position for approximately 1 cm. into the cervical canal after the cervix is steadied with a tenaculum. A rapid, slightly rotating motion bringing the cutting cups together will then secure a cone of tissue from the external os (Fig. 2). In patients with a wide, lacerated, multiparous os, it may be necessary to take several strokes with angulation of the curette to complete a circumferential sample. Such a maneuver is also wise in the patient with an erosion where the histologic external os does not coincide with the anatomical one. It is important to remember that a symmetrical instrument must be manipulated to take a general sample from an irregular surface.

Discomfort is minimal, no greater than that which is experienced with endometrial biopsy. We have noted undue bleeding on rare occasions. It is our custom to place an ordinary gauze tampon against the cervix after the biopsy and we have, on occasion, bolstered this for the friable, easily bleeding cervix with a pledget of oxidized cellulose gauze.

The healing of the biopsy area is always prompt and uneventful. In fact, we have occasionally seen the healing of a minor erosion following such a sampling in a similar manner to that which follows superficial cauterization. We have not seen cervical strictures of any nature.

In an effort to avoid complexity in the laboratory we have not made serial sections or special orientations of these blocks. We have made some effort to obtain coronal sections through the cone of tissue or coned tissue fragments and approximately 6 sections at representative levels through the block, in order to strike the squamous-columnar junction as frequently as possible by these simple means (Fig. 3).

Detection Rate

In this group of 500 women whose uteri offered neither symptoms nor signs of cervical malignancy, we have found 10 intraepithelial cancers; 10 other patients with basal-cell hyperplasia were also discovered. It may be of interest to inspect the summary of these cases in Tables I and II.

A recapitulation of the patients upon whom a diagnosis of intraepithelial cancer or basal-cell hyperplasia was made is presented in these tables, together with a representative positive area of the coning biopsy obtained in the former group. It is rather important to emphasize the difficulty of presenting an adequate histologic survey of any patient with one photomicrograph.

TABLE II. ENDOCERVICAL CONING BIOPSY. TOTAL GROUP SCREENED, 500 PATIENTS. SUSPICIOUS CERVICAL LESIONS DETECTED IN 10, OR 2 PER CENT

	AGE (YEARS)	SYMPTOMS		DIAGNOSIS		ENDOCERVICAL CONING BIOPSY	SMEAR
		GENERAL	PELVIC	GENERAL	PELVIC		
D. F.	34	Parathesia, fingers	0	Raynaud's disease	0	Basal-cell hyperplasia of cervix	III
L. A.	50	0	0	0	0	Basal-cell hyperplasia of cervix	III
S. C.	33	Lump in groin	0	Fibroma, canal of Nuck	Fibromyomas	Basal-cell hyperplasia of cervix	III
J. O.	25	Indigestion	0	No organic disease	0	Basal-cell hyperplasia of cervix (Fig. 14)	IV
R. P.	42	Low back pain	0	Orthopedic disease	Mild chronic cervicitis	Basal-cell hyperplasia of cervix	V
R. W.	59	Constipation	0	Rheumatoid arthritis	0	Basal-cell hyperplasia of cervix	I
R. M.	38	Check-up	0	Syphilis	Fibromyomata uteri Hypertrophy of cervix	Basal-cell hyperplasia—extreme	III
M. R.	35	Nervousness Weight loss	0	Thyrotoxicosis	Possible chronic salpingitis	Basal-cell hyperplasia	III
L. B.	40	Frequent colds	0	Allergic rhinitis	No gynecological disease	Basal-cell hyperplasia	I
A. B.	37	Lower abdomen pain	0	Anxiety state Irritable colon	Cervical erosion Possible salpingitis	Basal-cell hyperplasia	III

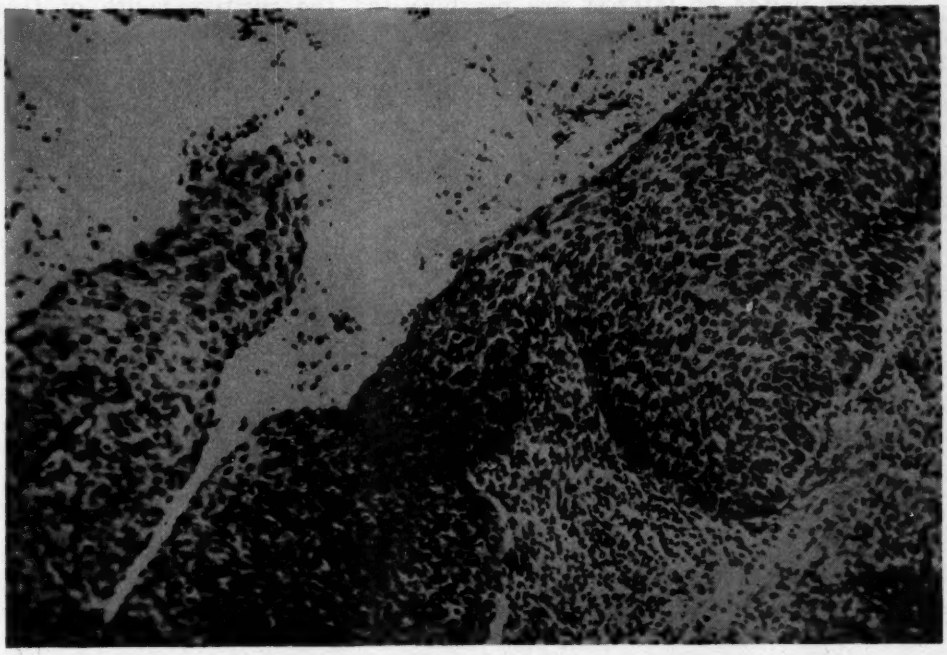

Fig. 7.—Intraepithelial carcinoma of cervix. Frequent tongues of breaking through basement membranes have occurred in other areas.

Fig. 8.—Intraepithelial carcinoma. Malignant change extends to surface and cytologic smear was also positive, though there is poor attempt at surface maturation in some places.

Several points of interest are notable: (a) the relative youth of these patients; (b) the close agreement between cytologic and biopsy studies; (c) early tongues of invasion found in 5 of these 10 intraepithelial lesions; (d) the variety of reasons that brought these patients under surveillance.

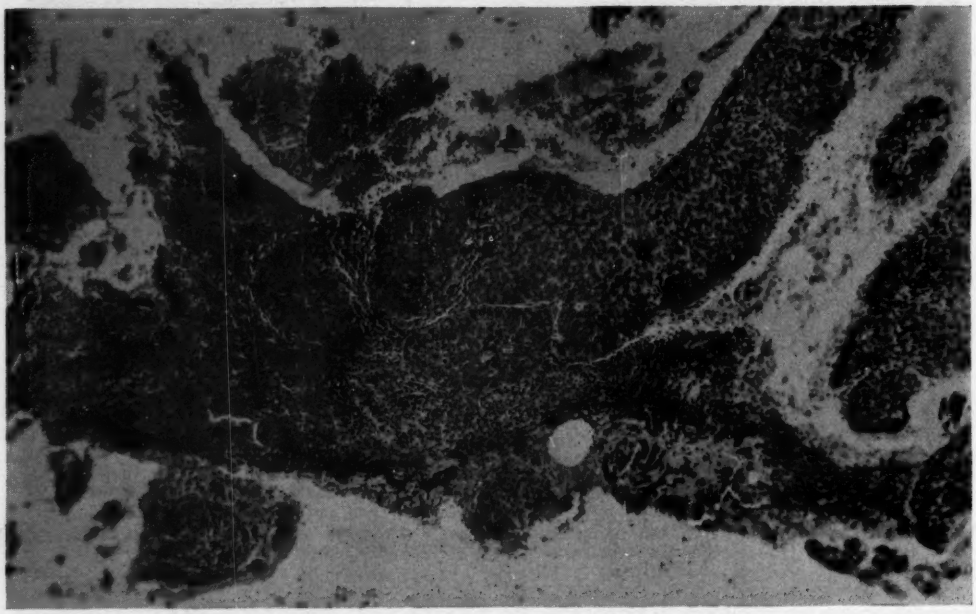

Fig. 9.—Intraepithelial carcinoma of cervix. Much surrounding inflammatory reaction in patient with chronic salpingitis.

Fig. 10.—Intraepithelial carcinoma of cervix. Areas of early invasion were also present.

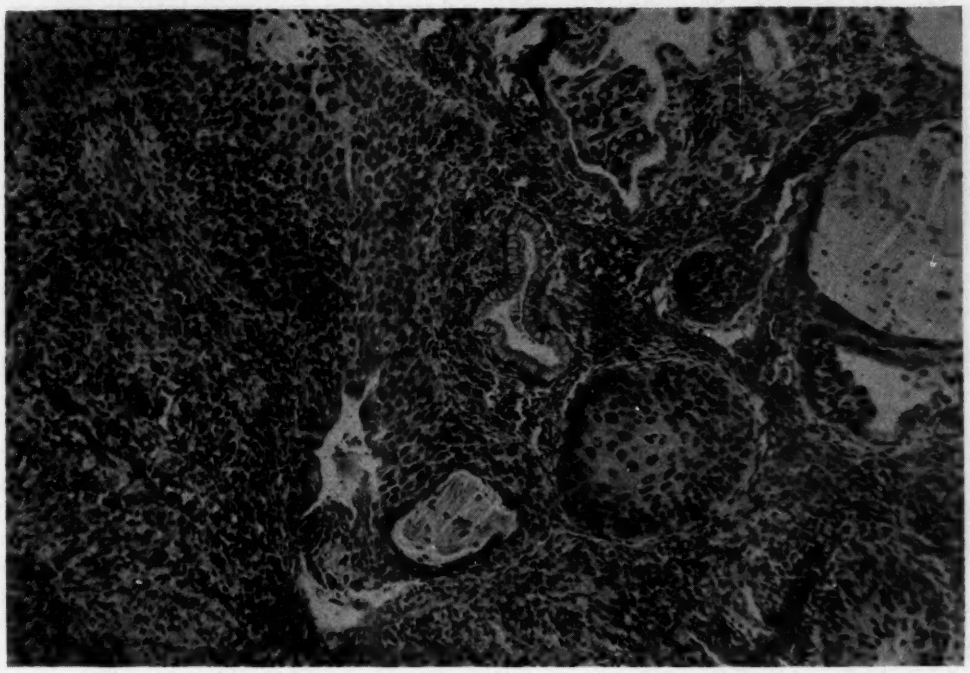

Fig. 11.—Intraepithelial carcinoma which is dipping down to replace many glands.

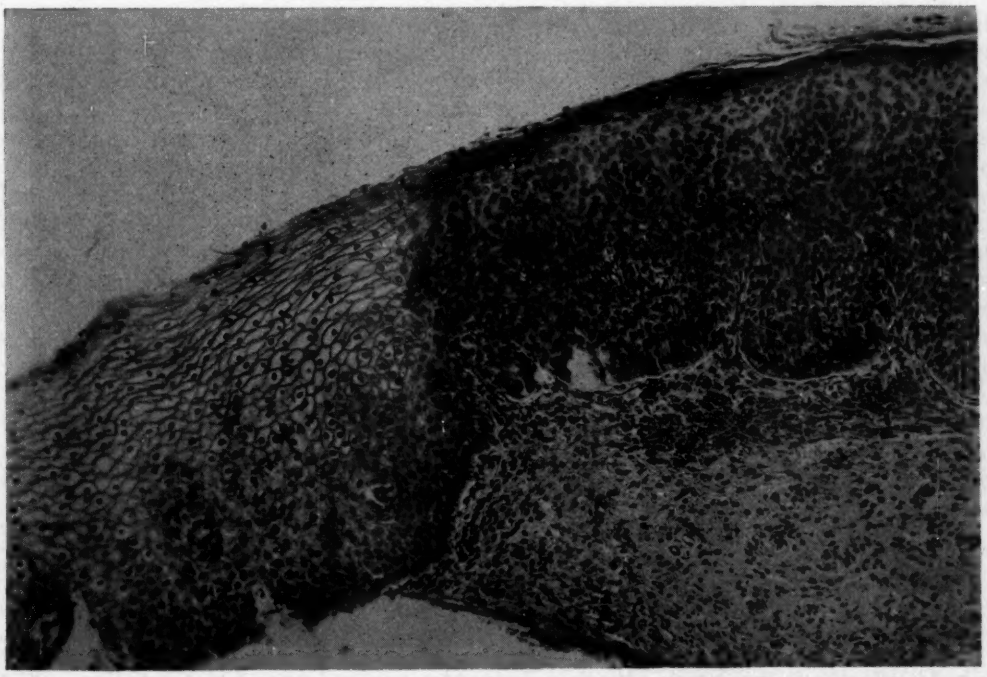

Fig. 12.—Intraepithelial carcinoma with areas of early invasion. Note abrupt change from normal to malignant epithelium, though in this area one can discern an attempt at surface maturation which is lost elsewhere.

Fig. 13.—Intraepithelial carcinoma.

Fig. 14.—Basal-cell hyperplasia. Surface maturation has been maintained; stripping effect is present in this area.

There is no reason to believe that the gynecological pathologist will require any significant orientation period to accustom himself to the interpretation of these sections. The biopsies are usually smaller than those taken with a scalpel under an anesthetic, but they contain the vital squamous-columnar region which is required for study and sufficient stroma to afford cellular background. We have had several instances where large punch or scalpel biopsies have missed the lesion and small coning biopsies have detected it. On infrequent occasions an extremely gritty or atrophic cervix may resist an adequate sample. It has been our experience that such a cervix which lacks sufficient friability to permit a proper biopsy rarely harbors a cancer. An intramucosal lesion will sometimes peel away from the underlying stroma; in such a case there will be no doubt of the malignant nature of the cervix on the coning biopsy but it may be necessary to supplement this technique with circumferential biopsy under anesthesia properly to evaluate invasiveness.

It may be important to emphasize here that these sections were studied by a group of pathologists and none but those with undoubted malignant change included. We have not presented any with debatable minimal disorganization such as is occasionally seen in squamous metaplasia and may be misinterpreted for intraepithelial cancer by the unwary. We have accepted the customary criteria for the diagnosis of basal-cell hyperplasia with malignant cellular disorientation and characteristic nuclear cancer change confined to the deeper epithelial layers with maturation of cells to normal on the surface (Fig. 14). Such apparent preservation of some physiologic control is of course lost in a true neoplasm like the intraepithelial carcinoma. We have found the cytologic smear a considerable aid in evaluating the nature of the most superficial layers.

Comment

This cervical cancer detection rate of 2 per cent in apparently normal women is not surprising in the light of pathological studies of apparently benign hysterectomy specimens where multiple sectioning disclosed an even higher percentage.[8] There is no doubt that preclinical cervical cancer may be discovered in a significant percentage of the female population by techniques now available to us. It is not within the province of this report to discuss the life history of intraepithelial cancer, but there is no longer much doubt that these lesions are truly malignant. We do not know how long it will take any individual lesion to invade and it may be possible that in rare instances, a patient might live out her lifetime without further advancement of the disease. It is clear, however, that the sooner we school ourselves to this evolutionary concept of cervical cancer, and adjust our diagnostic methods accordingly, the greater will be our reward in preventing such lesions from progressing to a stage where treatment is complex and frequently fails. The fact that it is easily possible to overtreat or mistreat patients with borderline or seedling lesions should in no way distract us from our search for these lesions and their precise definition. Certainly, no gynecologist who has watched his patient die of uncontrolled cervical cancer could seriously doubt the many advantages of enthusiasm for cervical biopsy.

Summary and Conclusion

1. A simple method of taking a circumferential coning biopsy of the squamous-columnar region of the cervix has been presented.

2. The importance of this region in the detection and definition of intraepithelial and early invasive cancer has been re-emphasized.

3. A survey of 500 gynecologically normal women by this technique has revealed a 2 per cent incidence of intraepithelial cancer, half of these already having started early tongues of invasion. A 2 per cent incidence of basal-cell hyperplasia was also noted.

4. The advantages of this method as a histologic corollary to cytologic techniques and as a primary scouting method have been presented.

5. It is clear that the addition of these detection methods can not only be clinically useful, but they may also teach us more about the evolutionary nature of this disease.

The author wishes to express his gratitude for the clinical assistance of Dr. David Moore and Dr. George Way of the Sloane Hospital Resident Staff. He is also greatly indebted to Miss Dorothy Graham and Miss Betty Newman for their able collaboration in the cytologic examinations.

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TOTAL ABDOMINAL AND VAGINAL HYSTERECTOMY, A COMPARISON*

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IN THE early years of abdominal pelvic surgery, "hysterectomy" implied removal of the corpus uteri with the cervix left in situ. After the technique of total abdominal hysterectomy became popularized, the literature contained numerous reports from various clinics comparing and analyzing the two methods. Some extolled one method and some the other. Today, even though we admit that subtotal hysterectomy has a small but definite place in the treatment of the diseased uterus, the majority of experienced gynecologists feel that total hysterectomy should be performed whenever possible. When the virtues of one operative procedure are compared with another, statistics are more valuable when they come from one group of competent surgeons with extensive experience in both methods. The statistical results will vary in any given group from year to year as techniques and the use of adjuncts to recovery improve. Thus, Siddall and Mack, in reviewing 6,692 abdominal hysterectomies performed at Harper Hospital from 1928 to 1945, showed a consistent lowering of the death rate from 3.7 per cent to 0.78 per cent. At the Mayo Clinic, Masson showed a higher mortality rate for total as against subtotal hysterectomy (1.2 per cent to 0.9 per cent) for the years 1934 to 1938; while McKinnon and Counseller from the same clinic showed a reversal of these figures a few years later (total 0.78 per cent, subtotal 1.04 per cent). It is therefore obvious that, when statistics are compared, the data used must take into consideration comparable periods in the development of the operative procedure, the ability of the surgeons whose cases are compared, and the type and extent of the pathologic conditions for which the operation is performed.

These factors must be kept in mind when the relative merits of abdominal as against the vaginal removal of the entire uterus for comparable indications are compared. One should not compare a series of vaginal hysterectomies done in 1949 with a series of total hysterectomies done 20 years previously. In some clinics the abdominal method has been practiced almost to the exclusion of the vaginal method, the latter being reserved for the treatment of prolapsus only. In other clinics the vaginal method has been highly developed and often performed with overenthusiasm. Such enthusiasts have even employed vaginal hysterectomy for the removal of far-advanced disease. The large group of experienced operators who utilize both methods with equanimity consider such a condition a contraindication to vaginal removal.

*Presented before the Chicago Gynecological Society, May 19, 1950.

There are many reports of the analyses of total and of vaginal hysterectomies in the literature from various clinics. These compare the statistics on total from one clinic with the statistics on vaginal hysterectomy from another. Our present analysis was undertaken to determine if there was any difference in morbidity between the two operations when performed for relatively comparable types of uterine pathologic conditions and in equal number by the *same* group of operators. Throughout the years certain ideas about the relative merits of the two operations have been expressed differently by different members of our staff. Some have stated that the morbidity of one operation was less than the other, that the removal of adnexa affected morbidity, that drainage reduced morbidity, etc. This study helped us to clarify our own thinking on the results of our own work.

Material

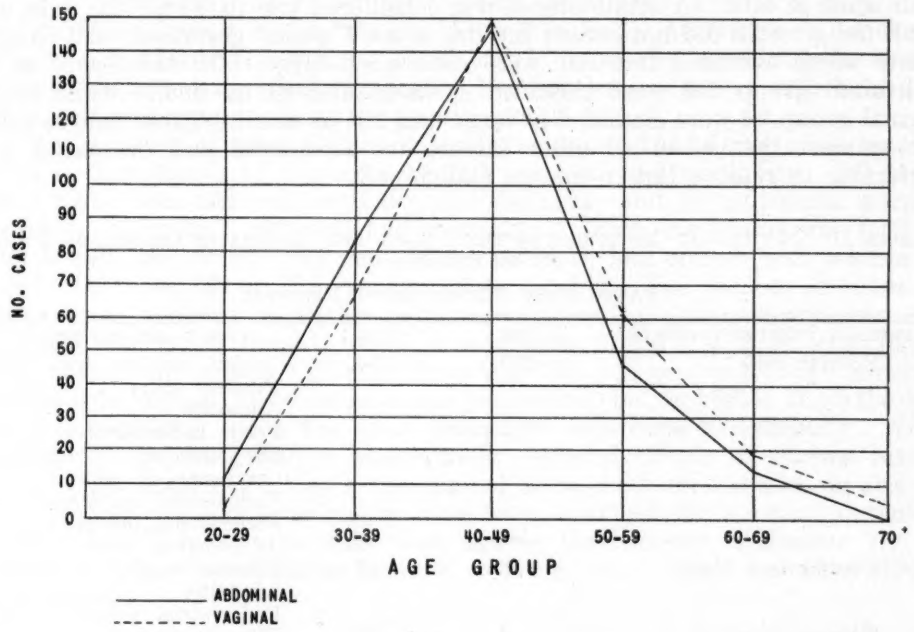
Starting with Jan. 1, 1946, 300 consecutive cases of total abdominal hysterectomy and 300 consecutive cases of vaginal hysterectomy performed at the Michael Reese Hospital were critically analyzed and compared. This was done in order to note the morbidity in each group and to determine whether, for relatively comparable conditions, one method was preferable to the other. The patients in this group were private patients and were operated on by members of the gynecological attending staff, who perform either operation with equal facility. Clinic patients, who are operated on by the Resident Staff under attending supervision, were not included in this analysis. There were 15 operators who performed the 600 operations (Table I). It is noted that those operators who did the greatest volume of work and who are considered the more experienced technicians removed the uterus vaginally somewhat more often than abdominally. The difference in numbers (245 versus 282) is not appreciable, and it may be concluded that, with this group of senior men, the route of operation was about equally divided. Among the men with lesser practice and experience, however, abdominal hysterectomy was done almost three times more often than vaginal hysterectomy (55 versus 18). It is our impression that as the experience of the operator increases, his indications for vaginal surgery broaden.

TABLE I. DIVISION OF CASES AMONG THE INDIVIDUAL SURGEONS
(600 HYSTERECTOMIES—300 ABDOMINAL; 300 VAGINAL)

SURGEON	TOTAL ABDOMINAL	VAGINAL	TOTAL
1	55	89	144
2	44	57	101
3	39	48	87
4	35	26	61
5	27	27	54
6	33	19	52
7	12	16	28
	245	282	527
8	15	2	17
9	9	4	13
10	13	0	13
11	8	5	13
12	4	5	9
13	3	1	4
14	2	1	3
15	1	0	1
	55	18	73
Total	300	300	600

The ages of the patients operated on in the two groups were compared (Fig. 1). As was to be expected, the greatest number fell into the age group 40-49 years and were equally divided (147 abdominal and 148 vaginal, total 295). In the younger group, age 20-39 years, 94 had abdominal hysterectomy performed and 68 had vaginal hysterectomy; while in the older group 50-69 years, 13 had abdominal and 23 vaginal hysterectomy. The reason for the greater incidence of vaginal hysterectomy in the 5th, 6th, and 7th decades is obvious, when we consider that it is in these periods that prolapsus is most common. Of the 300 patients operated on vaginally, 215 had reparative surgery in addition to the hysterectomy, and the need for this additional work is one of the more important indications for choosing the vaginal route.

FIGURE I. AGE-GROUP DISTRIBUTION OF HYSTERECTOMIES
(300 ABDOMINAL; 300 VAGINAL)



Parity seemed to be a deciding factor in the choice of method of removal of the uterus. In the total abdominal group, 103 patients were nonparous and 197 were parous; while in the vaginal group only 5 were nonparous and 295 were parous. We are not in agreement with those who feel that it is "easier to remove the uterus vaginally in a nullipara than in a multipara." Even though pelvic relaxation is not too important for removal of the uterus, it helps in the same way that the increased exposure of a larger incision facilitates abdominal surgery. It is true that a nullipara after vaginal hysterectomy is more comfortable than the parous patient whose relaxations necessitated wide dissection and repair. On occasion, we have had to increase exposure in a nullipara by a perineotomy. Our figure of 5 nulliparas in 300 vaginal hysterectomies is certainly small compared to Campbell's series of vaginal hysterectomies in which one-third of the patients were nulliparous. Our statistics indicate that, as a group, we prefer to remove the uterus abdominally in the nulliparous patient.

The size of the uterus and its contained pathologic abnormalities is often a deciding factor in the choice of the vaginal or abdominal method of removal.

In the opinion of the enthusiasts for vaginal hysterectomy, large and multiple benign tumors of the uterus are no contraindication, and growths extending above the umbilicus have been removed vaginally following morcellation. Others feel, as we do, that very large growths should be removed abdominally, unless the fibroids are definitely on the fundus or in the cul-de-sac and are demonstrably movable. With large multiple growths, it cannot always be determined on bimanual examination whether some of the fibroids are intraligamentous or not, or whether a hard ovarian tumor may be present and simulate a fibroid. In these situations, the abdominal route is preferable. There is no objection, should the vaginal approach prove impractical or dangerous, to completing the operation abdominally, but this necessity would obviously prove that the original judgment was in error.

For the sake of comparison, we arbitrarily divided the uteri removed into small and large. These data were derived from measurements included in the pathologist's reports and of course refer to the removed uterus, which is smaller than when in situ. A small uterus was considered one in which the sum total of all the growths did not exceed the size of an 8 weeks' gestation. All enlargements which exceeded this size were considered large. On this basis, in the abdominal group 219 were classified as large and 81 as small; while in the vaginal group 94 were classified as large and 206 as small. These figures reflect our opinion, that when all other fatcors are considered and evaluated, it is preferable to remove larger tumors abdominally.

TABLE II. PATHOLOGIC CONDITIONS IN THE UTERUS AND ASSOCIATED CONDITIONS FOUND AT SURGERY

(TAKEN FROM PATHOLOGIST'S REPORTS)

PRIMARY UTERINE PATHOLOGY	ABD.	VAG.	ASSOCIATED PATHOLOGY
Fibromyomas	219	194	Benign ovarian cysts Fibrosis ovary Adnexitis Pelvic endometriosis Carcinoma of the ovaries Carcinoma of tube Endometrial carcinoma Endometrial polyps Adenomyosis uteri
Adenomyosis uteri	16	16	Fibrosis ovaries Adnexitis Endometrial polyps
Fibrosis uteri	6	21	Fibrosis ovaries Adnexitis Endometrial polpyps
Endometrial polyps	12	22	Benign ovarian cysts Adnexitis Fibrosis ovaries
Endometrial carcinoma	8	1	Adnexitis Fibrosis ovaries
Endometrial sarcoma	0	1	
Normal uterus (menometrorrhagia)	36	44	Benign ovarian cysts Endometriosis of ovaries Pelvic endometriosis Fibrosis of ovaries Tuboovarian abscess Tuberculosis of tubes Hematometra
Pregnant uterus	3	1	Fibroids in 2 1 mistaken for fibroids 1 removed for sterilization
Total	300	300	

The chief symptoms of which the patients complained were bleeding, pain, and in the prolapsus cases, "pressure," and incontinence. No attempt was made to analyze the preoperative diagnoses, which in some instances were in variance with the findings, but an analysis of the pathologic findings reflects the indications for surgery (Table II). Fibromyomas were the chief reason for surgical intervention in both groups. All uterine conditions considered in this series, with the exception of endometrial carcinoma, were treated almost equally by the abdominal and vaginal route, thus making a comparison of the morbidities significant. Our study indicates that it is the other conditions such as adnexal disease, fixation, size of uterus, previous surgery, relaxations, carcinoma, etc., which determine whether a certain diseased uterus should be removed abdominally or vaginally.

Comparison of Morbidity

The standard of morbidity used was the usual one, namely, 100.4° F. on any two days postoperatively excluding the first 24 hours. This is a very strict standard taken from the obstetric morbidity standard. According to Jones and Doyle who established so-called "physiologic" norms for morbidity in hysterectomy, this is not an ideal standard. Nevertheless, it serves well here as a standard in comparison of one group with another.

In the series of total abdominal hysterectomies, the uterus alone was removed in 53 patients, of whom 13, or 24.5 per cent, had morbidity. When the uterus alone was removed vaginally (63 patients) and no additional surgery was done, 24, or 38.1 per cent, had morbidity. When the uterus was removed abdominally, 247, or 82.3 per cent of the patients, had one or both adnexa removed. Of these, 69, or 27.9 per cent, were morbid. The number of times the adnexa were removed vaginally without additional plastic surgery was only 22, or 7.3 per cent of the 300 cases. A morbidity figure of 40.9 per cent in this group is not appreciably different from the 38.1 per cent morbidity incurred when simple vaginal hysterectomy was performed, but is higher than the 27.9 per cent morbidity when the same procedure was done abdominally. Since most of the ovaries removed abdominally revealed simple or corpus luteum cysts, it may be surmised that if the vaginal cases had been operated on abdominally, perhaps more ovaries would have been sacrificed for minimal pathology (Table III). It is obvious from these figures, that, in our experience, the abdominal approach is somewhat safer in so far as the over-all morbidity figures are concerned.

TABLE III. COMPARISON OF MORBIDITY FOLLOWING ABDOMINAL AND VAGINAL HYSTERECTOMY

	NO.	MORBID CASES	% MORBIDITY
Abdominal.—			
Uterus alone	53	13	24.5
Uterus and adnexa (one or both)	247	69*	27.9
Total	300	82	27.3
Vaginal.—			
Uterus alone	63	24	38.1
Uterus and adnexa (one or both)	22	9	40.9
Total	85	33	38.8
Uterus plus anterior and/or posterior plastic	165	59	35.8
Uterus plus adnexa plus anterior and/or posterior plastic	40	21	52.5
Uterus plus ovarian resection plus anterior and/or posterior plastic	10	5	50.0
Total	300	118	39.3

*One death, pulmonary embolus.

There was no difference in morbidity in vaginal hysterectomy when in addition to removal of the uterus, an anterior and/or posterior colpoperineorrhaphy was done (38.1 per cent versus 35.8 per cent). However, when vaginal hysterectomy was combined with adnexal removal plus plastic procedures, the morbidity rose appreciably (52.5 per cent).

TABLE IV. PREVIOUS SURGERY IN PATIENTS OPERATED UPON BY THE ABDOMINAL ROUTE

Unilateral salpingo-oophorectomy		26 cases
Alone	11	
Plus appendectomy	15	
Bilateral salpingo-oophorectomy		1
Myomectomy		9
Alone	5	
Plus suspension	1	
Plus appendectomy	3	
Ventral suspension of the uterus		11
Alone	3	
Plus appendectomy	7	
Plus cholecystectomy	1	
Ovarian resection		6
Alone	4	
Plus appendectomy	2	
Salpingectomy		3
Unilateral	1	
Bilateral	2	
Tubal plastic operation		1
Exploratory laparotomy, pelvic inflammatory disease		1
Cesarean section		1
Suprapubic cystotomy		1
Radium insertion		1
Manchester operation		1
Cervical amputation		1
Vaginal plastic		1
Cholecystectomy		14
Alone	8	
Plus appendectomy	6	
Appendectomy		11
	Total	89

Previous surgery had been done in 89 patients who were subjected to total abdominal hysterectomy (29.7 per cent of the 300 cases). Only 53 of the patients subjected to vaginal hysterectomy had previous significant surgery (17.7 per cent of the 300 cases) (Tables IV and V). The effect of previous surgery on morbidity is analyzed in Table VI. There were 27 cases of morbidity in the abdominal group which had previous surgery (30.3 per cent) compared to the total morbidity in this group of 27.3 per cent. Of the 53 patients in the vaginal group who had had previous surgery, 20, or 37.7 per cent, had morbidity. This compares favorably with the over-all morbidity in this group of 39.3 per cent. It seems from the above statistics that the morbidity within each group is not affected by previous surgery. However, it must be emphasized that the choice of the vaginal route, where previous surgery has been done, is determined not by the type of the previous operation, but by the nature of postoperative residue, namely, fixation of the uterus, status of the adnexa, incisional hernia, etc.

A list of the causes of morbidity is given in Table VII. It is noted from the percentages given that urinary retention and urinary tract infection are considerably higher when the vaginal route is chosen. On the other hand, paralytic ileus, venous thrombosis, pulmonary embolus, and ureteral injury

were more frequent in the abdominal group. The unexplained fevers in both groups were about equal and if plotted would probably simulate the curve of "physiologic" norms for hysterectomy as set down by Jones. There was one death in the abdominal group. This 66-year-old nullipara had had a curettage performed 4 days before hysterectomy and a diagnosis of adenoma malignum was made at that time. Her postoperative course following panhysterectomy was not unusual except that she was slightly febrile for the first 5 days. Death occurred suddenly on the eighth postoperative day while the patient was out of bed. A large pulmonary embolus was fount at autopsy. In one patient in the abdominal group, a carcinoma of the tranverse colon was found at laparotomy, and was treated by resection and colostomy. The detection of unknown abdominal pathologic conditions is a valid argument in favor of abdominal hysterectomy.

TABLE V. PREVIOUS SURGERY IN PATIENTS OPERATED UPON BY THE VAGINAL ROUTE

Unilateral salpingo-oophorectomy		6 cases
Alone	2	
Plus appendectomy	4	
Myomectomy		5
Alone	4	
Plus appendectomy	1	
Ventral suspension of the uterus		4
Alone	3	
Plus oophorectomy	1	
Watkins interposition operation		1
Oophorectomy		2
Plus cervicectomy	1	
Plus appendectomy	1	
Transperitoneal nephropexy		1
Suprapubic cystotomy		1
Intestinal obstruction operation		1
Appendectomy		7
Cervical amputation		1
Vaginal plastic		1
Radium insertion		1
Cholecystectomy		21
Alone	8	
Plus appendectomy	13	
Subtotal gastric resection		1
	Total	53

TABLE VI. EFFECT OF PREVIOUS SURGERY ON MORBIDITY

	ABDOMINAL	VAGINAL
	(300 cases)	(300 cases)
Previous surgery	89 cases	53 cases
Morbidity	27 (30.3%)	20 (37.7%)
Total morbidity	82 (27.3%)	118 (39.3%)

Ureteral damage occurred twice in the abdominal group. In one, the left pelvic ureter was damaged, resulting in a ureterovaginal fistula, following total hysterectomy and bilateral salpingo-oophorectomy. This eventually healed spontaneously. In the other patient, the right ureter was sutured to the vagina in the repair of a tear in the anterior vaginal vault. The patient began to lose urine via the vagina within 24 hours of surgery. Pyelogram revealed the fistula to involve the ureter at its entrance into the bladder. Deligation of the involved stitch through the vagina produced spontaneous cure with restoration of the ureter and kidney pelvis to normal. The outcome of both of these cases was fortunate and does not represent the usual sequence of events when ureterovaginal fistula occurs, since many of these patients eventually require ne-

phrectomy. The ureter is liable to injury during vaginal hysterectomy when the adnexa are removed. The accident occurs when the course of the ureter is high in the posterior leaf of the broad ligament close to the infundibulopelvic ligament. Considering the removal of the uterus alone, it is less likely that the ureter will be compromised in vaginal than in abdominal total hysterectomy. The proximity of the uterine artery to the ureter presents a greater hazard to the latter when the uterus is removed from above downward.

TABLE VII. CAUSES OF MORBIDITY

	ABDOMINAL		VAGINAL	
	NO.	%	NO.	%
Urinary retention	41	13.7	65	21.7
Urinary tract infection	69	23.0	144	48.0
Paralytic ileus	10	3.3	2	0.7
Mechanical ileus	3	1.0	3	1.0
Wound infection	4	1.3	7	2.3
Wound disruption	1	0.3	0	0
Postoperative hemorrhage	3*	1.0	4	1.3
Venous thrombosis	3	1.0	1	0.3
Pulmonary embolus	2†	0.7	0	0
Peritonitis	2	0.7	1	0.3
Respiratory infection	3	1.0	0	0
Traumatic cystotomy	3	1.0	1	0.3
Ureteral injury	2	0.7	0	0
Unexplained fevers	25	8.3	22	7.3

*Two abdominal wall; one vaginal cuff.
†One death.

General anesthesia, cyclopropane and ethylene, supplemented on occasion by ether, was used most frequently in both groups. The data in Table VIII indicate that the patients in both groups fared somewhat better with spinal than with general anesthesia. The type of morbidity was practically similar in both groups, and there were no cases of frank pneumonia. There was no greater incidence of urinary retention when spinal was used than when general anesthesia was the anesthetic of choice.

TABLE VIII. ANESTHESIA AND MORBIDITY (600 CASES HYSTERECTOMY)

TYPE ANESTHESIA	NO. PATIENTS	MORBID	% MORBIDITY
Abdominal.—			
General	176	53	30.3
Spinal	107	23	21.5
Spinal plus general	16	6	37.5
Local	2	0	0
Total	300	82	27.3
Vaginal.—			
General	195	83	42.5
Spinal	93	31	33.4
Spinal plus general	3	1	33.3
Local	9	3	33.3
Total	300	118	39.3

An analysis of the use of drainage in both groups is shown in Table IX. The use of drains was employed chiefly by two of the surgeons. Surgeon No. 1 (Table I) performed the perponderant number of vaginal hysterectomies. He inserted a gauze drain into the peritoneal cavity. Surgeon No. 5 who performed an equal number of total and vaginal hysterectomies inserted a sulfonamide-

impregnated gauze drain between the vaginal vault and ligated stumps. In both instances the drain was removed after 36 to 48 hours. The statistics indicate that no reduction in morbidity was accomplished by drainage.

TABLE IX. VALUE OF DRAINAGE IN HYSTERECTOMY

	ABDOMINAL			VAGINAL		
	NO.	MORBID	% MORBIDITY	NO.	MORBID	% MORBIDITY
Drainage	84	21	25	133	51	38.3
No drainage	216	61	28	167	67	40.1
Total	300	82	27.3	300	118	39.3

Table X presents an analysis of the incidence of use of fluids, blood, chemotherapy, and antibiotics. Most of the patients received intravenous glucose in saline and water both during and after operation. When spinal anesthesia was used, intravenous fluids were always started with the onset of the surgery. This helped maintain the blood pressure and provided a ready means for the injection of vasoconstrictor drugs. One operator (Surgeon No. 2) does not use parenteral fluids routinely. An analysis of his cases showed a smaller incidence of urinary retention than the others. His contention is that an overdistention of the bladder is likely to occur when an excess of fluid is administered during surgery and postoperatively. Because of the anesthetic and analgesic drugs the overdistended bladder is less sensitive to the usual nerve reflexes. It is noted that blood transfusions were used three times more often in the abdominal group than in the vaginal group. This may be accounted for by the fact that, in many patients, the abdominal route was chosen because of larger and more vascular tumors and because of additional indications.

TABLE X. USE OF FLUIDS, BLOOD, CHEMOTHERAPY, ANTIBIOTICS

	ABDOMINAL		VAGINAL	
Fluids	259 Patients		242 Patients	
Blood	43		16	
Chemotherapy	60	Both in 15	142	Both in 30
Antibiotics	73		56	

Chemotherapy was used more than twice as often following vaginal than abdominal hysterectomy. This is explained by the greater incidence in this group of urinary tract infections and the use of retention catheters when plastic procedures were performed. The fact that the combination of both chemotherapeutic and antibiotic agents was used more often in vaginal than in abdominal hysterectomy is in keeping with the greater incidence of febrile morbidity in the vaginal group. In evaluating the use of these drugs, it must be stated that some operators used them prophylactically and at the slightest provocation. It is an unquestioned fact that the judicious use of blood and chemoantibiotic drugs has reduced the mortality rates of all surgical procedures in the past decade.

The average hospital stay for the abdominal group was 11.1 days, while the average for the vaginal group was 11.5 days, indicating no difference. However, there were more patients in the vaginal group required to remain over two weeks (40) than in the abdominal group (23).

Comment

We believe that vaginal hysterectomy should not be competitive with abdominal total hysterectomy as a means of removal of the diseased uterus. Each method has its own indications and contraindications. Each case should be evaluated individually, taking into consideration the type and extent of disease,

previous surgery, the presence of prolapsus. obesity, and the training and skill of the operator. In the comparison of the two groups in our series, it is shown that the over-all morbidity is greater in vaginal than in abdominal hysterectomy. However, the more serious postoperative complications such as ileus, thrombosis, embolism, and ureteral injuries are more frequent when the abdominal route is used. The only mortality (from pulmonary embolus) was in this group. Respiratory infections are more common in the abdominal group, but in this age of antibiotics, the possible occurrence of this complication should not be a deterrent to the use of this method. The hospital stay was the same in both groups and if this alone be taken as an indication of result, there should be no difference in choice of one method over the other, all other fatcors being considered. We believe that no gynecologist should be biased as to one or the other method. The well-trained and qualified gynecological surgeon should use both methods, basing his judgment on the individual case.

Conclusions

Vaginal and abdominal removal of the diseased uterus should not be competitive operations. The choice should be based on the sound and unbiased judgment of the gynecological surgeon, who is cognizant of the indications and contraindications present in each patient.

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Discussion

DR. AARON E. KANTER.—The time has now passed when one has to make an apology for using the vaginal approach for pelvic surgery. In my humble opinion an experienced, well-rounded gynecologist who does not use this accepted safe method in at least 25 to 50 per cent of his operations should not consider himself a fully experienced gynecological surgeon.

The general surgeons can see no reason for a specialty of gynecological surgery and I would be inclined to agree with them if as gynecologists we could not improve on the methods and techniques which they employ in the surgery of the female pelvis.

The essayists claim that their patients were operated on by members of the gynecological staff who are considered to be able to perform either operation with equal technical facility. Yet in their discussion they claim the experience of the surgeon increases his enthusiasm for the vaginal approach. Their more experienced surgeons did 245 abdominal operations against 282 vaginal, while their less experienced men did 55 abdominal hysterectomies against 18 vaginal. I would venture to say that, had the junior group had more experience, they too would have done more vaginal hysterectomies than abdominal.

Their statistics as to morbidity and mortality are comparable to the statistics published by other observers except in patients in whom adnexal disease was removed, where the morbidity was 51 per cent. This is too high; there should be no higher morbidity than that seen when the uterus was removed by morcellation. Since the use of the penicillin suppository the night before surgery and attempting to clean up all foci of infection before surgery, we have been able to keep our morbidity down to 10 per cent.

An experienced gynecologist should in advance of surgery be able to determine the feasibility of the vaginal approach. I agree with the essayists that each case must be decided upon by the condition present in that particular case and according to the experience of the particular operator. When the patient accepts service from a surgeon, the surgeon will serve her best if he chooses the approach by which he is most proficient. One may assume that there are individuals who cannot master the vaginal technique, who know the technique but whose results are poor. This is no reason for condemning the vaginal approach for all other operators.

Patients often tell us that other gynecologists whom they have consulted advised against the vaginal approach, actually telling the patients that the vaginal operator works in the dark and cannot completely explore the pelvis. If this were true the vaginal approach to pelvic surgery would never be indicated. One must explore the tubes, ovaries, and many times the rectosigmoid area. On the other hand, im exploration of the upper abdomen is indicated the method of approach should be abdominal.

Now as to abdominal versus vaginal hysterectomy, the only true, fair comparison of these two methods would be to take cases which could safely be done by either route, alternate the approach, and study the postoperative course from the viewpoint of morbidity and mortality. I can assure you, as all statistics show, the patients operated upon by the vaginal route will have less discomfort and less ileus, less phlebitis, less ureteral and vesical complications, and an earlier total convalescence. Let us assume that there is a little more morbidity of temperature in the vaginal cases, the lack of the more severe complications as mentioned above will surely offset the temperature morbidity of which in most cases the patient has no knowledge.

The essayists state that in other clinics the vaginal method has been developed and used with overenthusiasm. I suppose the Presbyterian Hospital Group, of which I am a member, would be included in this overenthusiastic group. I can assure you the proper approach for the surgery has been weighed with extreme care before the decision is made and our results certainly give us no reason for changing our views. After all, it is a matter of judgment, experience, and results. We take no unusual risks and, in event an error of judgment has been made, I can see no objection to completing the operation abdominally. In the last 15 years there has been no need in my experience to complete an operation by the abdominal route which was started vaginally. However, in the future should such an occasion arise I would not hesitate for a moment to change my plan, as discretion is the better part of valor.

I agree with the essayists that in by far the largest number of operations drainage is not necessary and drainage need only be done when there is uncontrollable oozing, when one unhappily enters into the bowel, or when one comes in contact with an active undiagnosed inflammatory process.

Vaginal hysterectomy is in no way competitive with the abdominal route. When one method or the other is decided upon, it is done so with mature judgment.

Hysterectomy by the vaginal route must not be considered free from complications. Any patient operated upon by the vaginal route may fall heir to any complication which may occur by the abdominal method. However, all statistics show that these complications are much less frequent when the surgery is done vaginally by one who is competent. Thus each approach has its indications, but if the conditions present make it possible to be done vaginally it is by far the safest and best method of approach.

DR. LEVENTHAL (Closing).—I agree with everything Dr. Kanter has said. There is one additional point I would like to make. I think it is a mistake for any gynecologist to make up his mind that he is going to do a case abdominally or vaginally, and then not reverse it with better judgment at the time of surgery. It might be best to tell the patient that the uterus will be removed vaginally but that it might have to be done abdominally. The patient should be examined under anesthesia before surgery is started. There may be found conditions which were not detected previously. There can be no criticism of the gynecologist who, for justifiable reason, changes his judgment at the last moment.

POSTERIOR COLPOTOMY: AN AID IN THE DIAGNOSIS AND TREATMENT OF ECTOPIC PREGNANCY*

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THE posterior colpotomy incision is a simple, safe procedure for the diagnosis of ectopic pregnancy and, frequently, the incision allows ample space for removal of the pregnancy. Since the diagnosis of ectopic pregnancy, particularly the unruptured ectopic pregnancy, is usually one of suspicion, any safe and simple procedure which definitely establishes the diagnosis should be of general use. However, in reviewing the literature, one discovers that, following the advent of aseptic surgery, the posterior colpotomy incision has been used by few surgeons and actually has been condemned by the majority. We hope to encourage more general acceptance of this valuable surgical procedure.

Our thesis is based upon the experience of the Obstetrical and Gynecological Staff of the Presbyterian Hospital in the diagnosis and treatment of 224 ectopic pregnancies during the years from January, 1920, to July, 1949.

Differential Diagnosis: By History, Physical and Laboratory Findings

Ectopic pregnancy is most commonly confused with early abortion, persistent corpus luteum cyst, and pelvic inflammatory disease, since these conditions not only give symptoms but also history and findings of the same general nature.

In review of our cases the history is a greater aid in the diagnosis of a suspected ectopic pregnancy than are physical and laboratory findings, although the history and findings in this group of patients do not differ from those reported and reviewed in the extensive literature on ectopic pregnancy. Any patient in the childbearing age who gives a history of temporary amenorrhea, disturbed bleeding, lower abdominal soreness, crampy or sharp pain, pain referred to the shoulder, or pain not infrequently related to the emptying of the bladder or bowel, and who may have had faintness or shock of varying degrees must first be suspected of having an ectopic pregnancy. Disturbed bleeding and any combination of these symptoms should suggest ectopic pregnancy, just as bleeding in the last trimester of pregnancy must be considered to be a placenta previa until proved otherwise.

Only 5 patients in this series did not have disturbed bleeding. Their amenorrhea varied from 35 to 90 days before surgery (average 54 days). They entered the hospital after acute attacks of pain in the lower abdomen of 6 to 36 hours' duration and presented a picture of shock from slight to moderate degree. In 2 of these 5 patients, the ectopic pregnancy was diagnosed and removed through posterior colpotomy incision. Usually the disturbed bleeding

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followed shortly after the date of the expected menses, but the time interval is not of statistical value because of patients' inaccuracy in remembering dates relating to menses. The longest period of amenorrhea was 210 days, followed by 60 days of bleeding, the diagnosis of abdominal pregnancy being made on a gall bladder film taken by the patient's family physician.

Pain was usually described as being crampy in character in the unruptured or aborting cases, and sharp to severe in those with rupture. Only 20 patients were in shock. Subjective symptoms of gestation were most often absent in the early extrauterine pregnancies.

The average age of the patients was 29.65 years, the youngest being 19 and the oldest 45 years of age.

There were 93 primigravidas and 131 multigravidas of whom 103 had had one or more children.

Eight patients had been operated upon previously for the removal of an extrauterine pregnancy.

The physical findings recorded a normal to slightly enlarged uterus. Seventy-three had palpable masses. Pain on motion of the cervix was present in nearly all and usually was referred to the side involved.

At surgery the ectopic pregnancy was found 124 times on the right side and 100 times on the left. The ectopic had ruptured in 116 cases and was unruptured or aborting in 108 cases. Three conditions are noteworthy in this group of 224 patients:

1. Only 20 patients were in shock,
2. Only 73 had palpable masses, and
3. Only 116, or 51 per cent, had ruptured ectopic pregnancies at the time of surgery.

Laboratory findings were of no particular aid in the diagnosis of a suspected ectopic pregnancy. The Friedman test, when negative, did not exclude pregnancy, and, when positive, the test only confirmed the suspicion of disturbed gestation. In this series the test was not recorded enough times to be of statistical value. The red blood count was of significance as an approximate index of the patient's general condition. The white blood count was 9,000 or lower in 81 cases, the lowest being 4,900; the highest white blood count was 23,500. The average was between 10,000 and 12,000. The temperature readings were normal in 50 per cent of the cases, the others were low grade 99 to 100° F.; only 29 patients had temperatures varying from 100 to 101.6° F. A low-grade temperature with a high white count was usually associated with profuse bleeding into the peritoneal cavity.

Surgical Diagnosis

While in a small group of patients a fairly definite diagnosis of ectopic pregnancy can be made from the history and findings alone, most often the diagnosis is one of a suspected ectopic pregnancy, the suspicion being confirmed only on visualization of the site of the pregnancy.

Colpopuncture was done only 8 times. In our experience the procedure is of limited value, since if blood is asiprated from the posterior cul-de-sac one has not differentiated ectopic pregnancy from any other cause of bleeding into the peritoneal cavity. Negative findings on colpopuncture may be obtained if the blood is clotted, the pregnancy is walled off by adhesions, or if the ectopic pregnancy is early. This occurred in 3 of our cases. In 2 patients in whom colpopuncture failed to show blood, the ectopic pregnancies ruptured 6 days later, the patients went into shock and were operated upon by laparotomy.

Fortunately, the third patient with negative colpopuncture findings had sufficient symptoms to warrant further investigation. A laparotomy was performed and a ruptured ectopic pregnancy was removed.

Blood was not found in the cul-de-sac of 5 patients whose ectopic pregnancies were visualized and removed through the posterior colpotomy incision.

We have had no experience with culdoscopy. We acknowledge that the positive diagnosis of ectopic pregnancy can be made with the aid of the culdoscope, but for us the posterior colpotomy incision has not only given us a positive diagnosis in 149 suspected cases but we have also been able to remove the lesion through the incision in 77 cases, or 34.37 per cent of the total number of ectopic pregnancies. Throughout the literature the posterior colpotomy incision has been condemned because of the danger of introducing infection into the peritoneal cavity. This has not been our experience in its use.

From April, 1947, through October, 1949, we have used the posterior colpotomy incision 93 times for the reasons shown in Table I.

TABLE I. REASONS FOR USE OF POSTERIOR COLPOTOMY INCISION IN 93 CASES FROM APRIL, 1947, THROUGH OCTOBER, 1949

Suspected ectopic pregnancy	46
Endometriosis	12
Diagnostic	10
Vaginal sterilization	25

The findings at operation are indicated in Table II.

TABLE II. FINDINGS AT OPERATION

When Done For Suspected Ectopic Pregnancy (46).—	
Ectopic pregnancy	17
Incomplete abortion (could not be diagnosed grossly by scrapings)	11
Persistent corpus luteum cyst	9
Microcystic disease of the ovaries	2
Pelvic inflammatory disease	4
Corpus luteum cyst and dermoid	1
Corpus luteum cyst and serous cystadenoma	1
Negative pelvis	1
When Done For Suspected Endometriosis (12).—	
Endometriosis	4
Microcystic disease of ovaries	5
Pelvic inflammatory disease	1
No pelvic abnormality	2
When Done For Diagnosis (10).—	
Microcystic disease of ovaries	3
Endometriosis	3
Pseudomucinous cystadenocarcinoma	1
Parovarian cyst	1
No pelvic abnormality	2

Laparotomy was necessary to treat the pathology visualized through the posterior colpotomy incision in 11 patients.

For ectopic pregnancy	7
Endometriosis	3
Pelvic inflammatory disease	1
Pseudomucinous cystadenocarcinoma	1
Parovarian cyst	1

If the 2 additional patients with extrauterine pregnancy treated during this period by straight laparotomy were included, there was a total of 19 extrauterine pregnancies. Nine required laparotomy for the removal of the ectopic

pregnancy whereas 10 pregnancies, or 25 per cent, were removed through the colpotomy incision.

In the group of 93 patients treated by colpotomy, or colpotomy with laparotomy, 81 were afrebile. Twelve patients had morbidity, as follows:

2 days	8 patients
3 days	1 patient
4 days	2 patients
7 days	1 patient

One of the patients with four days of morbidity had an extensive pseudomucinous cystadenocarcinoma with metastasis. The other had a ruptured ectopic pregnancy removed by laparotomy after a colpotomy incision and postoperatively there were physical and x-ray chest findings of infection in the right lower lobe of the lung. The patient with the longest period of morbidity, seven days, had a ruptured ectopic pregnancy removed by laparotomy after a colpotomy incision. She had a cold on admission and postoperatively developed a urinary tract infection.

It is generally agreed that there is no expectant treatment for extrauterine pregnancy. The surgical procedures that were used in the management of the 224 ectopic pregnancies are shown in Table III.

TABLE III. SURGICAL PROCEDURES USED IN THE MANAGEMENT OF THE 224 ECTOPIC PREGNANCIES

Ectopic pregnancy removed through posterior colpotomy incision	68
Ectopic pregnancy removed through posterior colpotomy incision plus additional vaginal surgery	9
Ectopic pregnancy removed through laparotomy incision:	
Preceded by colpopuncture	8
Preceded by posterior colpotomy	72
Ectopic pregnancy removed through laparotomy incision	31
In all of the above cases there had been a dilatation and curettage preceding the snrgery listed.	
Ectopic pregnancy removed, straight laparotomy	19
Ectopic pregnancy removed, straight laparotomy plus additional abdominal surgery	17

The patient with a diagnosis of a suspected ectopic pregnancy was prepared for surgery. Under general anesthesia, usually ethylene inhalation and, of late years, Pentothal Sodium intravenously combined with ethylene and oxygen inhalation, the cervix was dilated and the uterus curetted to rule out a disturbed intrauterine pregnancy. If insufficient scrapings were obtained to make a diagnosis, the posterior cul-de-sac was opened. Upon the opening of the cul-de-sac, the presence of fresh or old blood was noted. Then the tubes, ovaries, and uterus were inspected for the presence of disease. Inspection was facilitated by the use of the Heaney narrow-blade vaginal retractors and by grasping the posterior wall of the uterus with tenacula or uterine hooks so that the uterus could be manipulated to bring the adnexa into view. If the ectopic pregnancy was an early one, it was usually not only exposed without difficulty but was also removed without difficulty. Occasionally, fibrinous adhesions would hold an early ectopic pregnancy against neighboring structures. Not infrequently, these adhesions could be freed by gentle finger dissection, thereby securing mobility so that the ectopic pregnancy could be brought down to the incision and be removed.

It should be noted in this group that:

1. Relaxation of the vagina from multiparity is not essential to the use of the posterior colpotomy incision since 43 patients were nulliparas.

2. The ectopic pregnancies were diagnosed early and treated early since only 10 patients had a palpable mass and only 28 patients had rupture of the extrauterine pregnancy.

TABLE IV. ECTOPIC PREGNANCY REMOVED THROUGH POSTERIOR COLOPOTOMY INCISION (68)

Gravidity.—		
Primigravidas	33	
Multigravidas	35	
One child or more	25	
Duration of Pregnancy.—		
3 to 8 weeks		
Previous Surgery.—		
Appendectomy	13	(one with round ligament suspension)
Ovarian cyst	1	
Ectopic pregnancy	1	(removed vaginally)
Pelvic Findings.—		
Mass palpable	10	
Tenderness slight to exquisite	68	
Side Involved.—		
Right	37	
Left	31	
Condition of Tube.—		
Ruptured	28	
Unruptured or aborting	40	
Morbidity.—		
21 patients had a total of 85 days' temperature, varying from 2 to 13 days, average 4 days. One patient had a pelvic abscess drained on the eleventh postoperative day.		
47 patients were afebrile.		

TABLE V. ECTOPIC PREGNANCY REMOVED THROUGH POSTERIOR COLPOTOMY INCISION PLUS ADDITIONAL VAGINAL SURGERY (9)

Gravidity.—	
Primigravidas	2
Multigravidas	7
One child or more	7
Duration of Pregnancy.—	
3 to 7 weeks	
Previous Surgery.—	
Appendectomy	2
Appendectomy, round ligament suspension, and resection of endometriosis	1
Pelvic Findings.—	
Lemon-sized mass	1
Slight to moderate tenderness	9
Side Involved.—	
Right	8
Left	1
Condition of Tube.—	
Ruptured	4
Unruptured or aborting	5
Additional Vaginal Surgery.—	
Vaginal hysterectomy	3
Myomectomy	1
Anterior and posterior vaginal plastic	1
Ovary removed with involved tube	3
Bilateral salpingectomy	1
Morbidity.—	
3 patients had a total of 17 days, the patient with the vaginal plastic operation having 8 days. Average was 5.6 days.	
6 patients were afebrile.	

Diagnosis of early ectopic pregnancy will allow vaginal removal. These patients had a minimum of postoperative discomfort, and were able to resume normal activities much sooner than if a laparotomy had been performed.

There were nine patients who had other vaginal surgery in addition to the removal of the extrauterine pregnancy.

We believe that, generally, the removal of the ectopic pregnancy and the control of bleeding are all the surgery that should be done. Additional surgery should depend upon the condition of the patient, the pathology present, and the skill and experience of the operator.

Ectopic pregnancies were removed by laparotomy eight times after colpopuncture had been performed. Again, we would emphasize that we do not believe that colpopuncture is of value in establishing the positive diagnosis of ectopic pregnancy. Ectopic pregnancies were removed by laparotomy 72 times after the suspicion of extrauterine pregnancy was positively confirmed by visualization through the posterior colpotomy incision. In this group the findings were as follows:

TABLE VI. ECTOPIC PREGNANCY REMOVED THROUGH LAPAROTOMY INCISION PRECEDED BY COLPOPUNCTURE (8), OR POSTERIOR COLPOTOMY (72)

Gravidity.—		
Primigravidas	39	
Multigravidas	41	
One or more children	33	
Duration of Pregnancy.—		
4 to 10 weeks		
Previous Surgery.—		
Appendectomy	6	
Cesarean section	1	
Ectopic pregnancy	5	
Pelvic Findings.—		
Mass palpable	35	(largest 8 cm.)
Tenderness slight to rigidity	80	
Side Involved.—		
Right	47	
Left	33	
Condition of Tube.—		
Ruptured	46	
Unruptured or aborting	34	
Morbidity.—		
43 patients had a total of 166 days. Average was 3.6 days. The longest was 14 days, the patient had had an attempted criminal abortion two weeks before surgery		
36 patients were afebrile		
Mortality.—		
1 patient died 24 hours after surgery (also had hysterectomy)		

The ectopic pregnancies in this group were of longer duration. They are frequently misdiagnosed as pelvic inflammatory disease. The posterior colpotomy incision will give a positive diagnosis and prevent delay in treatment of extrauterine pregnancy. Unnecessary laparotomies, thereby, will be eliminated. Thirty-five patients had palpable adnexal masses, and rupture of the ectopic pregnancy had occurred in 46. Whereas, 43 patients had morbidity, which was a higher incidence than for those who had had vaginal removal of the extrauterine pregnancy, the morbidity compared favorably with that of the other groups who had had laparotomies for the removal of their extrauterine pregnancies. The one death will be discussed later. Earlier diagnosis in this group would have permitted removal of the pregnancy by the vaginal route.

In a group of 31 patients, after intrauterine pathology had been eliminated by dilatation and curettement, the extrauterine pregnancy was removed by

laparotomy. One patient had a double pregnancy with tubal rupture occurring six days after a dilatation and curettage for an incomplete abortion, which was proved microscopically.

TABLE VII. ECTOPIC PREGNANCY REMOVED THROUGH LAPAROTOMY INCISION (PRECEDED BY DILATATION AND CURETTAGE) (31)

Gravidity.—	
Primigravidas	13
Multigravidas	18
One child or more	15
Duration of Pregnancy.—	
3 to 8 weeks	
Previous Surgery.—	
Appendectomy	5
Tubal plastic	1
Ectopic pregnancy	1
Pelvic Findings.—	
Mass palpable	10
Tenderness	31
Side Involved.—	
Right	17
Left	14
Condition of Tube.—	
Ruptured	14
Unruptured or aborting	17
Morbidity.—	
16 patients had a total of 82 days, an average of 4.5 days, and the longest 23 days due to thrombophlebitis	
12 patients were afebrile	

In a group of 19 patients, one had an abdominal pregnancy diagnosed by x-ray. The others were diagnosed on history and physical findings suggesting the classical picture of ruptured ectopic pregnancy. We do not see many patients presenting this classical picture of ruptured extrauterine pregnancy, except those in whom acute symptoms develop early in the growth of the extrauterine pregnancy.

TABLE VIII. ECTOPIC PREGNANCY REMOVED BY STRAIGHT LAPAROTOMY (19)

Gravidity.—	
Primigravidas	3
Multigravidas	16
One child or more	11
Duration of Pregnancy.—	
3 to 6 weeks	
1 fetus papyraceus	
Previous Surgery.—	
Ectopic pregnancy	1
Pelvic Findings.—	
Mass palpable	3
Rigid abdomen	7
Tenderness	19
Side Involved.—	
Right	7
Left	12
Condition of Tube.—	
Ruptured	11
Unruptured or aborting	8
Morbidity.—	
12 patients had a total of 75 days, average was 6.2 days. The longest, 24 days, was caused by thrombophlebitis	
7 patients were afebrile	

TABLE IX. ECTOPIC PREGNANCY REMOVED BY STRAIGHT LAPAROTOMY PLUS ADDITIONAL ABDOMINAL SURGERY (17)

Gravidity.—	
Primigravidas	3
Multigravidas	14
One child or more	12
Duration of Pregnancy.—	
3 to 16 weeks	
Previous Surgery.—	
Appendectomy	2
Myomectomy	1
Pelvic Findings.—	
Mass palpable	14
Abdominal rigidity	3
Tenderness, abdominal	17
Side Involved.—	
Right	8
Left	9
Condition of Tube.—	
Ruptured	13
Unruptured or aborting	4
Additional Abdominal Surgery.—	
Hysterectomy	5
Appendectomy	7
Round ligament suspension	1
Defundectomy	2
Bilateral salpingectomy	7
Salpingo-oophorectomy	2
Bilateral oophorectomy	1
Morbidity.—	
14 patients had a total of 59 days. Average 4.2 days	
3 patients were afebrile	

TABLE X. ANALYSIS OF MORBIDITY

	TOTAL NUMBER	AFEBRILE	FEBRILE	NO. OF DAYS FEBRILE	PERCENTAGE FEBRILE	NO. OF FEBRILE DAYS DIVIDED BY TOTAL NUMBER OF PATIENTS TREATED
Ectopic pregnancy removed through posterior colpotomy incision	68	47	21	85	30.8	1.25
Ectopic pregnancy removed through posterior colpotomy incision plus additional surgery	9	6	3	17	33.3	1.88 days
Ectopic pregnancy removed by laparotomy after colpotomy or colpopuncture	80	36	43	166	53.7	2.07 days
Ectopic pregnancy removed by laparotomy after dilatation and curettage	31	12	19	82	61.2	2.64 days
Ectopic pregnancy removed by straight laparotomy	19	7	12	75	63.1	3.94 days
Ectopic pregnancy removed by straight laparotomy plus additional surgery	17	4	14	59	82.3	3.47 days

In a group of 17 patients the ectopic pregnancy was removed by straight laparotomy plus additional abdominal surgery (Table IX). This group had the highest incidence of rupture with hematoma formation producing a palpable mass. These patients also had the highest incidence of morbidity. While we cannot definitely state that the morbidity was entirely due to the additional surgery, we must conclude that any other surgery, except that of an emergency nature, should be postponed when the patient has an ectopic pregnancy.

Analysis of Morbidity

The morbidity in the 224 patients is analyzed in Table X.

Analysis of Mortality

The death reported (Case No. 249050) does not belong in the group of ectopic pregnancies diagnosed by colpotomy and treated by laparotomy because additional surgery, an abdominal hysterectomy, was performed at the time the ectopic pregnancy was removed.

This white woman, gravida iii, para ii, aged 33 years, was admitted to the hospital April 26, 1930. She gave a history of normal menstrual periods until the last one which was a week late and was characterized by four weeks of intermittent bleeding and lower abdominal cramps which at times were quite severe. The admission notes stated that she was not acutely ill, though the blood pressure was 90/60 and the temperature 101° F. The lower abdomen had a protective rigidity to palpation. The laboratory reported hemoglobin 45 per cent, red cells 3,000,000, and leucocytes 13,900. During the next four days of observation the temperature varied from 99° F. in the morning to 101.6° F. in the afternoon. A diagnosis was made of acute inflammatory disease of the pelvis and on May 1, 1930, a posterior colpotomy incision was made to drain what was thought to be a pelvic abscess, which had begun to bulge the posterior cul-de-sac. Old blood was encountered. A gauze drain was placed in the incision. A laparotomy was performed at which time a ruptured right tubal pregnancy with hematoma formation was removed and a hysterectomy also performed. Her postoperative condition was poor, stimulants and 3,000 c.c. of normal saline by hypodermoclysis failing to improve her condition. She expired twenty-four hours postoperatively during a blood transfusion, of which she had received 200 c.c. Autopsy was not permitted.

Death, directly or indirectly caused by hemorrhage, is preventable. Adequate blood transfusion before surgery, and chemotherapy when needed, will save the lives of many patients who have the misfortune to develop extrauterine pregnancies. However, it is our responsibility to diagnose and treat ectopic pregnancies early before acute symptoms develop.

Summary

1. An early positive diagnosis of extrauterine pregnancy based on history, physical examination, and laboratory findings can be made in only a small number of cases.

2. The value and safety of the posterior colpotomy incision in the diagnosis and treatment of 93 gynecological cases were reported.

3. Of the 224 ectopic pregnancies reported, the diagnosis was established for 149 cases by the use of the posterior colpotomy incision.

4. In 77, or 34.37 per cent of the 224 cases reported, the extrauterine pregnancy was diagnosed and removed through the posterior colpotomy incision.

Conclusions

1. The posterior colpotomy incision is a safe and useful procedure for the early positive diagnosis of ectopic pregnancy.

2. Early ectopic pregnancies can be removed safely through the posterior colpotomy incision, and when possible this is the best treatment.

3. When a laparotomy is necessary to remove an ectopic pregnancy visualized through the colpotomy incision, there is no increased risk to the patient.

4. Additional elective surgical procedures should not be performed at the same time an ectopic pregnancy is removed.

5. Early diagnosis and treatment of ectopic pregnancy will reduce mortality and morbidity to a minimum.

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Discussion

DR. ROBERT M. GRIER.—The authors have given an excellent report on the method of handling ectopic pregnancy at Presbyterian Hospital of Chicago. As might be expected, a vaginal approach to another gynecological problem is recommended. Their results, as usual, are very commendable. It would seem that the procedure can be done without too much difficulty.

The high percentage of cases which were treated without rupture seems remarkable, 108 in 224. But when the so-called aborting cases are included, this figure is misleading. To me a tubal abortion means that the embryonic sac has been separated from its attachment within the tube but has not broken through the serosa. Maybe it has escaped, or is attempting to escape through the fimbriated end. In either event the resulting loss of blood with peritoneal insult, pain, formation of a palpable mass, syncope, and shock can be just as formidable even though the serosa is still intact. I think, if we exclude these cases, the actual number of "unruptured" tubal pregnancies would be much smaller.

If I understand the authors correctly, all but 36 of their 224 cases, however treated, whether by laparotomy or through posterior colpotomy incision, were subjected to dilatation and curettage. This seems to me to be an unnecessary routine procedure. At the Evanston Hospital most of our cases are diagnosed without this and certainly rarely with the aid of colpotomy. I wonder how many early abortions were done inadvertently. I recall one case we had recently in which a woman was operated upon for a definite tubal pregnancy. She had previously had the other tube removed for ectopic pregnancy. Later, much to the surprise of her physician, a uterine pregnancy was discovered, which went on to term. A living child was the result. Routine curettage in this rare case would have been a catastrophe.

I also wonder why, in 80 cases out of 157, it was necessary to do laparotomy after a colpopuncture or posterior colpotomy, rather than removal through the colpotomy incision. Apparently better judgment would have been a laparotomy approach in the first place. What were the reasons for this further approach from above?

The authors admit that a good history plays the most important part in making a diagnosis of ectopic pregnancy. They state that, when amenorrhea, disturbed bleeding, crampy pains, shoulder pain, or shock are present, one should be suspicious of ectopic pregnancy. I believe that with this story a definite diagnosis could have been made, especially with shoulder pain and any degree of shock. Certainly, it should be required infrequently to submit these women to the additional trauma of dilatation and curettage and/or colpotomy and then, so many times, proceed to laparotomy. However, today, with free use of blood transfusions and chemotherapy and antibiotics, we can "get away" with many things.

The analysis of morbidity is significant but the variation for the different procedures was not too striking because the number of febrile days ranged only in average from 1½ to 3½ days. Laparotomy approach alone showed the most morbidity but I venture to say that these were the most seriously ill patients. Had they been submitted to the added trauma of dilatation and curettage and/or colpotomy, the morbidity in these cases would have been still higher. They have also shown from their figures that additional surgery done in conjunction with operation for ectopic pregnancy carries with it risk of greater morbidity, even when this additional surgery is done only through the colpotomy incision. With this we all agree.

I believe that, in certain early cases, when the patient's general condition is not too critical and when great doubt exists, colpotomy can be a definite aid in diagnosis of ectopic pregnancy. Nevertheless, it has always seemed to me that in the visualization of the tubes through a colpotomy incision, when tenaculi and uterine hooks are required to pull the fundus posteriorly into view, and when, in many cases, the tubes must be grasped with Allis forceps, or "what have you," unnecessary and perhaps permanent damage may be done to normal tubes.

What is the disadvantage in making a small laparotomy incision for clinching the diagnosis? More adequate exposure is afforded with less trauma. If necessary, immediate extension can be made and better exposure obtained. If the pregnancy is in the cornu, certainly, the approach is ideal for the required surgery. If the pregnancy is in the uterus, prompt closure does not interfere with gestation. If an abortion is incomplete or in progress, no harm has been done, even if a dilatation and curettage are indicated later.

If the death described in this series of 224 cases is the only one, it is an enviable mortality record. In a series of 100 consecutive cases, reported from the Evanston Hospital, we had three deaths. Like the one reported here, these patients today would in all probability have been saved. Massive hemorrhage is usually the principal cause of death. Since 1936 there has been one death in 84 more cases. This was an abdominal pregnancy.

DR. EDWIN J. DE COSTA.—Drs. Draa and Baum have emphasized the great value of posterior colpotomy not only as a diagnostic procedure but as an avenue of therapeutic approach. I wonder if they have considered anterior colpotomy for similar purposes? We find that, if the uterus is antepoised or the round ligament shortened, vaginal sterilization is greatly facilitated.

I would question the authors' division of tubal pregnancies into ruptured and unruptured or aborting. It seems that the symptomatology and findings of tubal abortion are so closely associated with intraperitoneal hemorrhage that the grouping with unruptured tubal pregnancy is undesirable.

I would further question the need of resorting to colpotomy in order to establish a diagnosis in 67.5 per cent of their patients (149 out of 224 patients). In addition, it will be remembered that where colpotomy was performed for suspected ectotpic pregnancy, the diagnosis was correct in only 37 per cent (17 out of 46 patients). Added together, this might indicate that colpotomy was resorted to whenever the operators were in doubt and that doubt as to diagnosis often existed.

But things are not always as they seem. Actually this indicates an ever conscious respect for ectopic pregnancy and the utilization of every means to establish a diagnosis. This is the main reason that there was only one death in 224 cases of ectopic pregnancy—an enviable record. The authors are to be congratulated.

DR. ALEXANDER GABRIELLIANZ.—In cases where there is a suspected ectopic pregnancy and the patient is hospitalized, I think it would be correct to do an Aschheim-Zondek test. There may be no time to wait but diagnostically it is necessary to prove the diagnosis.

DR. EDWARD ALLEN.—I believe that Dr. Draa and Dr. Baum might have called this paper "The Diagnosis of Early Ectopic Pregnancy." Their aim has been to bring out the possibility of very early diagnosis by the free use of colpotomy. They have also pointed out the safety of the procedure in competent hands. Since about one-fourth of these patients have no palpable masses, colpotomy made the diagnosis possible before the usual palpatory evidence was present. The free use of colpotomy has saved me many restless hours of worrying about patients and saved a great many of them from tubal rupture and intra-abdominal hemorrhage.

One of my first papers at this Society was concerned with ectopic pregnancy and the use of colpotomy. In the discussion of that paper several of the older gynecologists were very critical about opening the cul-de-sac into an abdomen containing free blood. I am convinced there is no more risk in opening an abdomen containing blood from a ruptured ectopic pregnancy through the vagina than there is of opening the vagina and spilling blood during a hysterectomy. I believe we should speak out against depending entirely on colpopuncture. In many of the cases reported there was not sufficient blood to pick up by colpopuncture and in several more the shed blood was surrounded by omentum and bowel. Posterior colpotomy has no blind spots and leads to a positive diagnosis. It also affords a safe feasible approach to about one-third of the ectopic pregnancies treated; allows accurate differential diagnosis, as well as permits adequate treatment for many of the important lesions which closely simulate ectopic pregnancy.

DR. BAUM (Closing).—To answer Dr. Grier's question, we also have had patients who previously had been operated upon for ectopic pregnancy but who subsequently had normal intrauterine pregnancies. We have not interrupted normal uterine pregnancy by colpotomy incision. However, we feel we have saved a good many patients from having a ruptured tubal pregnancy. It is a much simpler operation, with less trauma and less shock to the patient, to open the cul-de-sac to diagnose an ectopic pregnancy than it is to make a buttonhole incision in the abdomen, and a buttonhole incision in the abdominal wall does not allow the same visualization.

Of the patients with posterior colpotomy only 73 had masses. In most of these patients we had difficulty in deciding whether they had ectopic pregnancy. We saw very few with all the diagnostic symptoms. There were only 20 patients who entered the hospital in shock.

As far as treating cornual pregnancy through posterior colpotomy, it can be done because the diagnosis is made early. It is as easy as doing a cornual resection for sterilization. One of the patients in this series had a cornual pregnancy resected through a posterior colpotomy incision and has since had a normal term pregnancy.

In regard to the anterior colpotomy incision, it is not desirable. The posterior colpotomy incision is best because it does not interfere with the bladder and the posterior colpotomy is the easiest place through which one can then enter the abdomen. It is a relatively simple procedure.

As to the question of the value of the Aschheim-Zondek test in determining whether the patient has an ectopic pregnancy, if the Aschheim-Zondek is positive we can assume that the patient is pregnant but we do not know whether or not it is an ectopic pregnancy. A negative Aschheim-Zondek test does not exclude an ectopic pregnancy, and we are likely to have a false sense of security.

Since there can be no expectant treatment for extrauterine pregnancy, and since an early positive diagnosis of unruptured extrauterine pregnancy based on history, physical examination, and laboratory findings can be made in only a small number of cases, we have offered this report of our experience to demonstrate the value of the posterior colpotomy incision.

THE RACIAL INCIDENCE AND MORTALITY OF ECTOPIC PREGNANCY

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FEW studies on the racial incidence of ectopic pregnancy have been published. In regard to its general frequency, the figure most often quoted is that of Schumann, namely, one ectopic to 303 intrauterine gestations. This ratio was obtained in the following manner. With the cooperation of the obstetrical and gynecological services of all hospitals in the city of Philadelphia, Schumann ascertained the total number of ectopic pregnancies observed in these hospitals during the year 1918 and compared this figure with the total number of births registered by the Bureau of Vital Statistics for the same period in the registered population of Philadelphia. The resultant data were as follows:

Cases of ectopic pregnancy in Philadelphia, 1918-1919	169
Birth registered during same period	45,153
Ratio of ectopic pregnancies to births	1:267

This ratio was then corrected in two ways. In the first place, the number of ectopic pregnancies which were actually diagnosed (169) was augmented by 10 per cent to account for patients who died at home from the complication under a mistaken diagnosis or who recovered without hospital aid or surgical interference. In the second place, in order to secure a figure for the total number of pregnancies during the period surveyed, the figure cited for registered births was augmented by 25 per cent to account for abortions. This 25 per cent correction was based on the data of Hirst. With these two corrections, Schumann obtained the following data:

Cases of ectopic pregnancy diagnosed plus 10 per cent	186
Registered births during same period plus 25 per cent	56,441
Ratio of extrauterine to intrauterine pregnancies	1:303

Schumann did not investigate the racial frequency of ectopic pregnancy and only a few reports on this subject are available. Perhaps the largest experience was reported by Beacham, Collins, Thomas, and Beacham. Their data are summarized in Table I which shows the number of ectopic gestations in relation to the number of deliveries in that institution in ten-year periods over a forty-year span, 1906-1946. This ratio for the entire period of time was 1:109 in Negro patients, whereas in white patients it was 1:65. However, in the same period of time the ratio of ectopic gestations to gynecologic admissions was slightly greater in Negro women (1:113 admissions) than in white gynecologic patients (1:139 admissions.) Nucci was unable to detect any difference in racial incidence in a study of ectopic pregnancy in Pittsburgh. Allen holds the same opinion but presents no statistics to support this veiwpoint. The unreliability

of individual hospital statistics for the question at hand is demonstrated if the above data are compared with the Baltimore study of Wynne. In 1919 the latter author showed that among 22,688 patients admitted to the Gynecological Department of the Johns Hopkins Hospital, 17,412 women were of the white race with 202 ectopic pregnancies (1:86 admissions), while 5,276 were Negroes with 101 ectopic gestations (1:52 admissions). From these data it might be concluded that extrauterine pregnancy is more common in Negro women. Hence, the data of individual hospitals may be grossly misleading as indices of the racial frequency of ectopic pregnancy, due apparently to such factors as the relative availability of beds for white and Negro patients and other special circumstances governing hospital admission.

TABLE I. RACIAL COMPARISON OF THE INCIDENCE OF ECTOPIC PREGNANCY AT THE CHARITY HOSPITAL, NEW ORLEANS

YEARS	WHITE			NEGRO		
	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO
1906-1916	51	2,048	1:40	49	2,769	1:56
1917-1926	100	3,583	1:36	125	6,370	1:51
1927-1936	161	9,336	1:58	192	18,063	1:94
1937-1946	134	13,985	1:104	247	40,023	1:162
Total	446	28,952	1:65	613	67,225	1:110

Whether ectopic pregnancy is more frequent in white or in Negro women is a question of much more than academic interest for it has to do with the very etiology of the condition. Thus, it is generally held that one of the commonest causes of ectopic gestation is pelvic inflammatory disease. Since the latter condition, by general consensus, is more common in Negro women, one would expect ectopic pregnancy to be more common in that race. On the other hand, if extrauterine gestation is more common in white women, some doubt would be cast on the importance of pelvic inflammatory disease in the etiology of ectopic pregnancy.

In view of the unsatisfactory state of our knowledge concerning the racial incidence of ectopic pregnancy and because of the importance of the question, it seemed desirable to study it anew by Schumann's method of approach in a large city where both races exist in sufficient numbers to permit of statistical analysis. It seemed also worth while to check Schumann's data of 1918 in order to ascertain whether the same ratio of extrauterine to intrauterine pregnancy exists today as it did 30 years ago. Finally such a study promised to yield information about the mortality rate which is associated with this complication under modern methods of care.

Present Study

With the valuable aid of the record librarians, resident physicians, and chiefs of obstetrical and gynecological services of 19 hospitals within the population registration area of the city of Baltimore, the racial incidence of ectopic pregnancy in relation to total births during five years (1944-1948) was determined. These data, as reported by individual hospitals, are recorded in Table II. This list records every hospital registered to accept patients and in two instances no patients with ectopic pregnancies were admitted during the period of this study. It is believed that all diagnosed cases of ectopic preg-

nancy in Baltimore over the five-year span are included in this table. The wide variation in incidence recorded in Table II shows again how unreliable individual hospital statistics can be in revealing the actual racial incidence of ectopic pregnancy. The ratios of ectopic gestations to total births in white patients varied from 1:111 to 1:269. The variation in Negro patients was even more extreme with values from 1:31 to 1:862. This can be explained by the fact that 18 of the 19 hospitals admit white patients, whereas only 4 of the 19 admit Negro patients for delivery, and 6 of the 19 admit a Negro only for a surgical emergency.

TABLE II. THE RACIAL INCIDENCE OF ECTOPIC PREGNANCY TO BIRTHS IN 19 BALTIMORE HOSPITALS DURING A FIVE-YEAR PERIOD (1944-1948)

HOSPITAL	WHITE			NEGRO			COMBINED RACIAL		
	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO
Baltimore City	13	1,745	1:134	7	6,034	1:862	20	7,779	1:389
Bon Secours	44	5,202	1:118	0	0	-	44	5,202	1:118
Church Home	25	5,081	1:203	0	0	-	25	5,081	1:203
Doctors	0	637	-	0	0	-	0	637	-
Franklin Square	37	6,849	1:185	3	0	-	40	6,849	1:171
Johns Hopkins	58	6,428	1:111	152	4,692	1:31	210	11,120	1:53
Maryland General	27	4,559	1:169	0	0	-	27	4,559	1:169
Mercy	31	7,641	1:246	5	0	-	36	7,641	1:212
Provident	0	0	-	33	4,765	1:144	33	4,765	1:144
Sinai	85	10,324	1:121	0	0	-	85	10,324	1:121
South Baltimore	29	4,663	1:161	2	0	-	31	4,663	1:150
Saint Agnes	63	7,043	1:112	0	0	-	63	7,043	1:112
Saint Joseph	53	6,432	1:121	10	0	-	63	6,432	1:102
Union Memorial	23	5,476	1:238	0	0	-	23	5,476	1:238
University of Maryland	34	6,676	1:196	45	4,367	1:97	79	11,043	1:140
U. S. Marine	2	1	-	1	0	-	3	1	-
Volunteers of America	0	1,377	-	0	0	-	0	1,377	-
West Baltimore	53	8,106	1:153	0	0	-	53	8,106	1:153
Women's	27	7,273	1:269	0	0	-	27	7,273	1:269
Total	604	95,513	1:158	258	19,858	1:77	862	115,371	1:134

The racial incidence of ectopic pregnancy to total deliveries in the 19 Baltimore hospitals during the five-year period (1944-1948) was 1:158 in the white group and 1:77 in Negro patients. The yearly racial incidence varied slightly as illustrated in Table III. Since these ratios represented only hospital statistics, an attempt was made to correlate ectopic pregnancies with the total births during the same period in the population registration area for the entire city of Baltimore. These data were kindly supplied by Dr. Thurber Fales of the Statistical Section of the Baltimore City Health Department. In Table IV the racial incidence of ectopic pregnancies to total births in the city of Baltimore during the period is shown with a ratio of 1:160 for the combined

TABLE III. YEARLY RACIAL INCIDENCE OF ECTOPIC PREGNANCY TO TOTAL BIRTHS IN BALTIMORE HOSPITALS (1944-1948)

YEAR	WHITE			NEGRO			COMBINED		
	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO
1944	113	16,138	1:143	45	3,065	1:68	158	19,203	1:121
1945	100	16,248	1:162	50	3,296	1:66	150	19,544	1:130
1946	139	19,940	1:143	36	3,868	1:107	175	23,808	1:136
1947	134	22,555	1:168	54	4,506	1:83	188	27,061	1:144
1948	118	20,632	1:175	73	5,123	1:70	191	25,755	1:135
Total	604	95,513	1:158	258	19,858	1:77	862	115,371	1:134

white and Negro races. There was one ectopic gestation to 177 total births in white patients as compared to one ectopic pregnancy to 120 total births in the Negro women. This would indicate that ectopic pregnancy is more frequent in Negro than in white women, at least in Baltimore.

TABLE IV. RACIAL INCIDENCE OF ECTOPIC PREGNANCY TO TOTAL BIRTHS IN BALTIMORE CITY DURING THE YEARS 1944-1948

YEAR	WHITE			NEGRO			COMBINED		
	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO	ECTOPIC	BIRTHS	RATIO
1944	113	19,152	1:169	45	5,349	1:119	158	24,501	1:155
1945	100	18,487	1:185	50	5,199	1:104	150	23,686	1:158
1946	139	22,050	1:159	36	6,070	1:169	175	28,120	1:161
1947	134	25,023	1:187	54	6,999	1:130	188	32,022	1:170
1948	118	22,106	1:187	73	7,493	1:103	191	29,599	1:155
Total	604	106,818	1:177	258	31,110	1:120	862	137,928	1:160

It is informative also to compare the incidence of ectopic pregnancy to population ratios. Baltimore's population during the period 1944-1948 averaged 940,400, of which 188,000, or approximately 20 per cent, were Negroes. However, the total number of ectopic pregnancies in Negresses was 29.9 per cent of the total cases, that is, 50 per cent more than would be expected if the incidence had been the same in the two races. The percentage of total births which was Negro was 22 per cent. Accordingly, even by population and total birth analysis, there are relatively more Negro than white women with ectopic gestation in the city of Baltimore.

TABLE V. COMPARISON OF THE INCIDENCE OF ECTOPIC PREGNANCIES TO INTRAUTERINE PREGNANCIES IN THREE LARGE AMERICAN CITIES, PHILADELPHIA, HARTFORD, AND BALTIMORE

AUTHOR AND YEAR OF STUDY	REPORTED CASES			CORRECTED DATA SCHUMANN'S METHOD		
	ECTOPIC	BIRTHS	RATIO	ECTOPIC (+ 10%)	BIRTHS (+ 25%)	RATIO
Schumann (1918)	169	45,153	1:267	186	56,441	1:303
Miller						
(1909-1928)	565	62,913	1:111	621	78,641	1:127
(1929-1944)	357	69,704	1:195	392	87,130	1:222
Anderson (1944-1948)						
White	604	106,818	1:177	664	133,522	1:201
Negro	258	31,110	1:120	283	38,887	1:137
Combined	862	137,928	1:160	947	172,409	1:182
Total	1953	315,698	1:162	2146	394,621	1:184

In an attempt to correlate and compare our ratio of 1 ectopic to 160 deliveries with Schumann's corrected ratio, an additional 10 per cent was added to the number of ectopic pregnancies and 25 per cent was added to the total number of births as illustrated in Table V. The data of J. R. Miller who studied this problem in Hartford, Conn., were also incorporated in the table and submitted to similar analysis and correction. As is shown in the table, the figure obtained by Schumann of one extrauterine pregnancy to 303 intrauterine pregnancies is greater than Miller's ratio or the author's corrected value of 1:182 obtained by Schumann's method. If all four series are combined the corrected ratio is 1:184.

It may be argued that the two correction factors of Schumann, that is, 10 per cent for undiagnosed ectopic pregnancies and 25 per cent for abortions,

are too rigid and do not represent present-day conditions. The accuracy of vital statistics has improved during these three decades and certainly in Baltimore the cooperation between the Medical Examiner's office and the Vital Statistics section of the City Health Department would eliminate, within the limits of human error, the deaths from ectopic pregnancy at home. The actual number of cases of ectopic gestation which are undiagnosed and untreated but do not end fatally will probably never be known. Although every gynecological pathological laboratory accumulates a number of cases of hematosalpinx of undiagnosed etiology, the exact number preceded by tubal pregnancy also will probably never be established. Undoubtedly a modern woman with lower abdominal pain does not remain at home as long as she did 30 years ago and present-day surgery with its increasing safety does not delay laparotomy as may well have occurred occasionally in 1918. It is possible that these factors have augmented the frequency with which the diagnosis of ectopic pregnancy has been made in recent years.

For obvious reasons the frequency of abortion can never be reliably known and varies from urban to rural areas. At the present time a value of 25 per cent used as the correction factor by Schumann is probably too high. Studies by Dunn indicate a figure of 1 abortion to every 5.6 confinements or about 18 per cent in urban areas. Whelpton in a weighted average study of several representative samples from several predominantly white cities, derived a figure of 14.4 per cent. Tietze investigated the incidence of abortion on the obstetric service of the Johns Hopkins Hospital and arrived at a figure of 17 per cent of pregnancies ending in abortion.

If it be true that Schumann's correction factor for abortions is too high and if the alternative figure of 15 per cent be employed instead (retaining his 10 per cent correction for undiagnosed ectopic pregnancies), the resultant data in the present series are as follows:

RACE	TOTAL ECTOPICS PLUS 10 PER CENT	TOTAL DELIVERIES PLUS 15 PER CENT	RATIO ECTOPICS: TOTAL PREGNANCIES
White	664	122,841	1:185
Negro	283	35,775	1:126
Combined	947	158,616	1:167

In view of all the above data it would seem probable that the actual incidence of ectopic gestation is greater than Schumann's statistics would indicate and that the true ratio in white women is in the general neighborhood of 1:190 pregnancies and in Negro women 1:130 pregnancies. On the basis of these data, as well as the population figures already cited, it would appear also that ectopic pregnancy is about 50 per cent more common in Negro than in white women.

Gordon's study of a series of 3,343 cases of ectopic pregnancy collected from the American literature between 1925-1935 showed a mortality rate averaging 4.6 per cent. It was interesting, therefore, to compare the mortality of ectopic pregnancy in our two large racial groups and to ascertain whether appreciable reductions in mortality have been made. The number of deaths were compiled from several sources such as the hospitals, the City Health Department, and the Baltimore Maternal Mortality Committee Reports and were carefully checked. As demonstrated in Table VI, the mortality from ectopic pregnancy during the five-year period from 1944-1948 was 0.7 per cent for white patients and 3.9 per cent for Negroes, with a combined racial mortality of 1.6 per cent (862 cases with 14 deaths). Twelve of these 14 fatalities occurred in the hospitals of Baltimore, while two patients died at home, the diagnoses being verified by the coroner's autopsies. Individual hospital mortality percentages varied from zero to 9 per cent. Ten private hospitals had no deaths in 427 ectopic preg-

nancies. Ten of the 14 deaths were in Negro women. Six of the 14 deaths, or 42 per cent, were voted preventable by the Baltimore Maternal Mortality Committee. Seven patients received no blood at all, and interesting is the fact that 3 of the women were in the hospital from 11 to 72 hours with a diagnosis of ectopic pregnancy but without operative therapy over this period.

TABLE VI. ECTOPIC PREGNANCY MORTALITY IN THE CITY OF BALTIMORE, MARYLAND, 1944-1948

	WHITE			NEGRO			TOTAL WHITE AND NEGRO		
YEAR	ECTOPIC	DEATHS	% MORTALITY	ECTOPIC	DEATHS	% MORTALITY	ECTOPIC	DEATHS	% MORTALITY
1944	113	2	1.8	45	2	4.4	158	4	2.5
1945	100	0	-	50	3	6.0	150	3	2.0
1946	139	1	0.7	36	2	5.5	175	3	1.7
1947	134	0	-	54	2	3.7	188	2	1.0
1948	118	1	0.8	73	1	1.4	191	2	1.0
Total	604	4	0.7	258	10	3.9	862	14	1.6

During the five-year period there has been a steady decrease in the mortality rate, and in the last two years of the study the total mortality rate in Baltimore from ectopic pregnancy has fallen to 1 per cent. One of the best hospital mortality rates reported is the series of Marchetti, Kuder, and Kuder who had only one death in 141 cases of ectopic pregnancy, or a rate of 0.71 per cent. Although the following data may not be statistically comparable they show that a low ectopic mortality may be obtained even under diversified conditions.

STUDY	ECTOPIC PREGNANCIES	DEATHS	PER CENT MORTALITY
Beacham, Collins, Thomas, and Beacham (1937-1946)	134 White	2	1.4
	247 Negro	9	3.6
Charity Hospital	381 Total	11	2.89
Anderson (1944-1948)	604 White	4	0.7
	258 Negro	10	3.9
City of Baltimore	862 Total	14	1.60

Beacham and his group, working with strictly charity patients in the South's largest hospital, feel that education of the laity on early and adequate prenatal care, institution of the residency system and adequate administration of blood have greatly reduced the mortality of ectopic gestation. As in all maternal mortality data, Negroes have a greater mortality than the white race. This is well borne out by the study of Williams and Corbit who analyzed 2,204 ectopic gestations recorded by hospitals and the coroner's office in the city of Philadelphia from 1931-1943. In this large group of ectopic pregnancies 101 fatalities occurred, or a mortality of 4.6 per cent. However, in the last two years of this study the mortality was 2.2 per cent. In this survey Williams and Corbit found that the ratio of ectopic deaths to puerperal deaths was twice as high in Negroes as in the white race.

Although this study does not differentiate the problem of advanced extrauterine pregnancy or abdominal pregnancy, it is desirable to point out Beacham and Beacham's study of 20 cases with a white incidence of one abdominal pregnancy to 11,419 deliveries as compared to a Negro incidence of 1 abdominal pregnancy to 685 deliveries. Douglass and Kohn studied 26 cases of abdominal pregnancy in the population registration area of Baltimore and found 1 abdominal pregnancy to 67,534 live births in the white group compared to 1 ab-

dominal pregnancy to 4,188 live births in the Negro race. They also found the mortality to be higher in the Negro group as compared to the white cases. Ware in Richmond had 13 cases of late extrauterine pregnancy, all in Negroes, in a clinic in which only one-half of the obstetrical patients admitted are Negroes. Early ectopic pregnancy occurred in the same percentage of white and Negro patients in his series.

Comment

This study indicates that ectopic pregnancy is more frequent in the Negro woman than in the white woman by about 50 per cent. Of the many causes which have been cited to explain the etiology of ectopic pregnancy, chronic pelvic inflammatory disease has been specified as the most prominent of the factors which delay or prevent the passage of the fertilized egg into the uterine cavity. Bernhard analyzed 645 cases of ectopic pregnancy and came to the conclusion that tubal changes following gonorrheal infection, abortion, or the use of contraceptives, and appendicitis were the most frequent etiological factors. Mahfouz in 1938 reported that in 50 per cent of his cases of tubal pregnancy there was a history of previous salpingitis and sterility. Other authors such as Tyrone, Romano, and Collins, and Johnson have substantiated these facts regarding the common association of salpingitis and ectopic pregnancy.

On the other hand, other authors find that salpingitis plays a less important role in the etiology of ectopic pregnancy and point out, moreover, that the effusion of blood in the condition may cause irritative changes which simulate histologically the picture of salpingits. Van Etten found that only 10.4 per cent of the patents studied by him showed signs of previous or concurrent tubal inflammation. In MacFarlane and Sparling's series of 110 cases, only 17.2 per cent of the patients gave a history of pelvic infection, while less than 10 per cent of the specimens examined by Litzenberg showed salpingitis when subjected to pathological examination.

Edward Allen, moreover, has adduced various evidence to support the viewpoint that salpingitis is an infrequent cause of tubal pregnancy. Thus he emphasizes such circumstances as the mobility of the affected tube in early ectopic pregnancy, the absence of external evidence of firm adhesions to the serosal coat of the tube, and the normalcy of the tubal mucous membrane at some distance from the site of implantation. To summarize all this evidence, including the author's study, it seems probable that salpingitis, although an important cause of tubal pregnancy, is responsible for only a minority of the cases, perhaps one-fourth.

Osiakina-Rojdestvenskaia has studied the tubes from 100 patients with tubal gestation by a meticulous histologic technique which made it possible for him to examine all the obstacles which might have interfered with the progress of the ovum and all the changes in the various layers along the entire length of the tube. He lists the etiological factors in this series as follows: defective tubal development of postembryonic origin, 21 cases; adhesions between tubal folds due to insufficient differentiation of the tubal mucous membrane, 21 cases; adenomyosis, 19 cases; inflammation 14 cases; and tumors, 3 cases. Seventy-six of the 100 cases, accordingly, were the result of mechanical obstacles in the tube. Ten additional cases are explained on the ground that external migration of the ovum had occurred with the result that the ovum had time to develop its capacity to implant before reaching the uterus. Of the 14 cases attributed to inflammatory changes in the tube, six were due to perisalpingitis. In such cases the author found, in addition to adhesions which caused curvature of the tube, numerous scars in the muscular tissue which doubtless interfered with motor activity. Partial obliteration of the tubal lumen secondary to inflam-

matory processes he encountered in only 3 cases. The author concludes that the most important factor in the causation of ectopic pregnancy is defective postembryonic development of the tube.

The pertinence of the racial findings in the present paper to the role played by pelvic inflammatory disease in the etiology of ectopic pregnancy will obviously depend on whether gonorrheal salpingitis is more common in Negro women. It is widely held, of course, that Neisserian infection is decidedly more common in Negroes but this is difficult of proof. Vonderlehr and Usilton in 1937 showed that the annual incidence rate for acute gonorrhea in white women in cities of 500,000 to 1,000,000 population was 4.7 cases per 1,000 persons as compared to 9.9 per 1,000 population in Negro women. In Baltimore during the year 1947, there were 224 cases of gonorrhea reported in white as compared to 649 cases in Negro women.

In view of the above data and many other statistics indicating a high incidence of gonorreal infection and of pelvic inflammatory diseases in Negro women, the conclusions would seem inescapable that the differential in racial incidence of ectopic pregnancy reported in this paper is attributable to a higher incidence of pelvic inflammatory disease in Negresses. By the same token, the racial data presented lend support to the viewpoint that pelvic inflammatory disease is an important factor in the causation of extrauterine pregnancy. If this be true, the more efficacious methods of treating gonorrheal infection now in widespread use may well lead to a reduction in the incidence of this frequent and grave complication of pregnancy.

Summary

The most often quoted incidence of ectopic pregnancy is that of Schumann, namely, one ectopic to 303 intrauterine gestations. This ratio was obtained from data in Philadelphia hospitals during the year 1918. It seemed worth while to check Schumann's data in order to ascertain whether the same ratio of extrauterine to intrauterine pregnancy exists today as it did 30 years ago. In addition, because of the unsatisfactory state of our knowledge concerning the racial incidence of ectopic pregnancy, it seemed desirable to study it anew by Schumann's method of approach in a large city where both races exist in sufficient numbers to permit statistical analysis.

During a period of five years (1944-1948) there were 862 ectopic pregnancies in 19 Baltimore hospitals. The unreliability of individual hospital statistics was shown in variations from ratios of ectopic gestations to total births in white patients from 1:111 to 1:269, and in Negroes from 1:31 to 1:862. Therefore ectopic pregnancies were compared with total births in the same period, in the entire population registration area of the city of Baltimore. There was one ectopic gestation to 177 total births in white women, as compared to one ectopic pregnancy to 120 total births in Negro women. Even by population and total birth analysis, there is approximately a 50 per cent higher incidence of Negro than white women with ectopic gestation in the city of Baltimore.

Using the correction factors of Schumann it would seem probable that the actual incidence of ectopic gestation is greater than Schumann's statistics would indicate; and that the true ratio in white women is in the general neighborhood of 1:190 pregnancies and in Negro women 1:130 pregnancies.

The mortality from ectopic pregnancy during the five-year period from 1944-1948 was 0.7 per cent for white patients, and 3.9 per cent for Negroes, with a combined racial mortality of 1.6 per cent (862 cases with 14 deaths).

The role of chronic inflammatory disease was discussed in its relation to the etiology of ectopic pregnancy. In view of the high incidence of gonorrheal infection in Negro women, the conclusions would seem inescapable that the differential in racial incidence of ectopic pregnancy reported in this paper is attributable to a higher incidence of pelvic inflammatory disease in Negroes. If this be true, the more efficacious methods of treating gonorrheal infection now in widespread use may well lead to a reduction in the incidence of this frequent and grave complication of pregnancy.

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OVARIAN VEIN PRESSURE STUDIES

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IN THIS paper attention is invited to the ovarian veins. This study is based mainly upon local ovarian vein pressures obtained at the operating table prior to pelvic surgery. Three standardized operating table positions were used. For the first, venous pressure was recorded with the table horizontal; the second, with the table slanted head upward 15 degrees; the third, with the table slanted head downward 15 degrees. In some instances observations were recorded with the operating table slanted head downward 20 degrees. Because this study was aimed at recording normal ovarian vein pressures, the patients were selected. The presence of extensive pelvic pathologic conditions such as adhesions and large tumors excluded studies on a large number of patients. Three patients were pregnant. Three were suffering from severe disturbances of the circulatory system. The remainder were in comparatively good health except for pelvic disease which showed no suggestion of producing obstruction to the ovarian venous return. In this fashion a comparative series of local ovarian venous pressure observations was obtained. It was felt that such information would lead to a better understanding of gynecological physiology and serve as a basis for further study.

Interest in this phase of physiology stems from confusing statements in the literature. The alleged difference between the pressure carried in the right gonadal vein contrasted to that carried in the left is generally held to account for the increased frequency of left varicocele in the male. The free anastomosis between the right and left broad ligament veins makes the laterality less evident in the female. According to Fagarsanu,[1] such reasoning was based upon anatomical dissection and dates from the times of Morgagni and Sir Astley Cooper. Another confusing point of interest was encountered in a recent study by Hodgkinson and Christensen[2] on ruptured uteroovarian veins during pregnancy. Analysis of the 75 cases reported suggested that increased ovarian vein pressure was a dominant etiological factor. If this were the case then the left vein would be expected to be the site of rupture more frequently than the right. In this group of cases where the point of vein rupture could be identified, the right vein was the site of rupture 28 times and the left 19 times. Other points of interest to the obstetrician-gynecologist are the presence, or absence, of competent valves in the ovarian veins, the response of local ovarian vein pressure to hydrostatic changes in pressure, and the ovarian vein pressure during pregnancy.

Apparatus

The apparatus consisted of the standard Becton-Dickinson spinal water manometer with an inside bore of 2 mm. Appropriate rubber tubing was used for connecting the manometer with a three-way stopcock, a 10 c.c. Luer syringe,

and the needle. The needle used was a Becton-Dickinson, two hole, malleable, 19 gauge, continuous spinal needle. Saline solution containing 5 c.c. of heparin in 1,000 c.c. of normal saline solution was used for filling the apparatus.

Material

The total number of patients studied was 31. Local ovarian vein pressures were accomplished in the left vein 26 times and the right vein 22 times. Three vein pressure observations, each taken with the operating table in a different position, were recorded in each vein studied, bringing the total number of observations to 165.

Procedure

After the abdomen was opened the ovarian plexus in the broad ligament was exposed and a large vein selected for study. The needle was inserted into the lumen of the vein and tied in place. All retractors and packs were removed from the abdomen and the ovarian vein and other abdominal viscera were allowed to assume their normal positions. All hands were removed from the abdominal wall as it was noticed that outside pressure caused the ovarian vein pressure to rise. Certain precautions concerning the state of anesthesia were observed. If the patient was under the influence of a general anesthetic, care was taken to be certain that the airway was free and the patient not straining. Sharp deviations of arterial pressure are known to influence venous pressure and were avoided. This feature was especially observed when spinal anesthesia[3, 4] was used.

The first reading was taken with the operating table in the horizontal position. The zero position of the manometer was fixed at the same level as the ovarian vein, and this position was maintained when readings were recorded with the operating table in the other positions. The second reading was recorded with the operating table slanted head upward at a 15 degree inclination. The third reading was recorded with the operating table slanted head downward 15 degrees from the horizontal position. When a fourth reading was taken, the operating table was slanted head downward 20 degrees. A Pitkin tiltometer attached to the operating table insured accurate table positions.

Results

Venous pressures taken with patients in the horizontal position with the zero level of the manometer at the level of the ovarian vein averaged 14.82 cm. of water. The highest pressure reading was 27 cm. of water in the right vein. The lowest pressure reading, 7 cm., was observed in the left ovarian vein. When the average venous pressure on the right was compared to that on the left no significant difference was noted. These averages were, left, 14.55 and right, 14.71 cm. of water pressure.

It was observed that the ovarian vein level closely approximated the right auricular level as determined by Lyons, Kennedy, and Burwell.[5] This proved to be about 10 cm. from the level of the operating table mattress taking into consideration the depression caused by the weight of the patient. Because of these conditions, ovarian vein pressure with the patient in the horizontal position represented central venous pressure as well as local ovarian vein pressure. These results serve for comparison with peripheral venous pressure studies performed by others.[6, 7, 8]

Fifteen Degree Slant, Head Upward.—With the operating table slanted head upward 15 degrees, the venous pressure was observed to rise sharply. Because the zero position of the manometer was maintained in its original po-

sition the right auricle was elevated above the zero position of the manometer. This maneuver provided opportunity for observing the effects of hydrostatic changes of a positive nature. The average ovarian venous pressure with the patient in this position was 19.66 cm. of water. Pressure in the right ovarian vein was 20.24 as contrasted to 19.18 cm. of water pressure in the left ovarian vein. The spread of observations extended from a high of 39.8 observed in the right ovarian vein to 9.0 observed in the left vein. In practically every instance the rise in vein pressure was abrupt.

Fifteen Degree Slant, Head Downward.—When the operating table was slanted head downward 15 degrees, the ovarian vein pressure promptly fell. In this position the zero level of the manometer was elevated above the level of the right auricle giving opportunity to observe negative hydrostatic pressure effects. The average venous pressure was 8.18 cm. of water. Venous pressure on the left averaged 8.13 and on the right 8.25 cm. of water. Pressure readings varied from a high of 18.4 on the right to a low of zero on both the right and left sides.

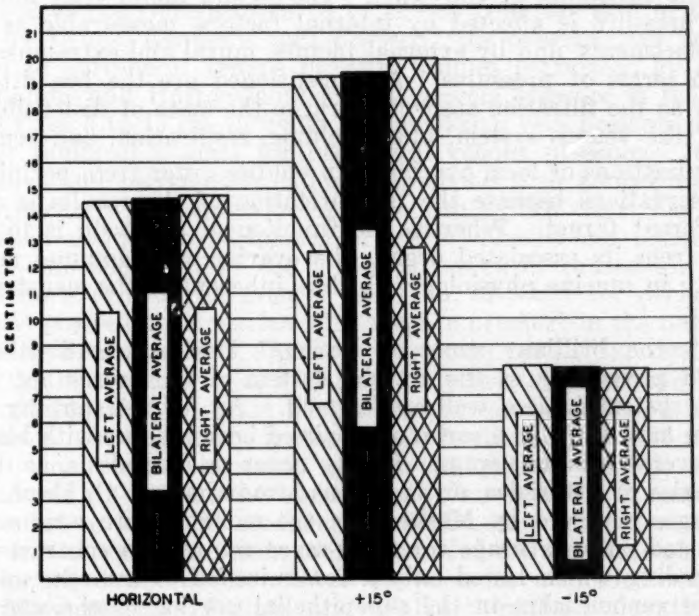

Fig. 1.—Average ovarian vein pressures:
Horizontal: Operating table horizontal.
Plus 15 degrees: Operating table slanted head upward 15 degrees.
Minus 15 degrees: Operating table slanted head downward 15 degrees.

Twenty Degree Slant, Head Downward.—In 11 patients additional venous pressure observations were recorded with the operating table slanted head downward 20 degrees. This position corresponds to the tilt of the table commonly used when gynecological surgery is performed, although the plane of the body was not broken at the knees as in the true Trendelenburg position. An unexpected reaction in ovarian vein pressure was observed. In 11 patients, 21 ovarian vein pressures were recorded. The pressure was elevated above that observed in the 15 degree slanting position in 7 instances, remained the same in 2, and demonstrated a further fall in 12 observations. The average of both sides was 9.64 cm. of water. The average pressure on the left was 9.12 and

on the right 10.11 cm. of water. This paradoxical pressure change was mainly due to 2 patients who were suffering from severe circulatory changes.

In these results no correction has been made for capillary attraction. With the solution used, this was tested to be 1.6 cm. of water. The true ovarian vein pressure is, therefore, 1.6 cm. of water pressure less than that reported.

Comment

In the past, studies on venous pressure have been concerned mainly with evaluating the functional state of the deeper and less accessible parts of the circulatory system. Landis and Hortenstine[9] in an extensive review emphasized the limited value of such studies. They pointed out that peripheral venous pressure is the final result of many complex physiological processes and mentioned the quadrilateral interplay of factors most important to venous pressure. According to them the following two general categories are noted. First, the blood enters the venules with appreciable vis a tergo and is met by the vis a fronte which includes the resistance to the flow on the part of the veins themselves and the resistance of the heart. The second factor they noted was how the venous pressure is affected by internal factors, measurable as volumes or volume displacements, and by external factors, mural and extramural, generally measured in terms of pressures. Also mentioned are the less directly acting factors such as the filtration-absorption ratio, the state of distensibility or contractility of the venous system, blood volume, respiration, and renal function.

The implications of local ovarian vein studies differ from peripheral venous pressure observations because the interpretation of the results is aimed at an entirely different target. Whereas the function of any vein is to drain away used blood from its associated organ, the ovarian vein assumes an additional responsibility in uterine physiology which is inherent in the menstrual function of the uterus.

Through the brilliant work of Daron,[10] Markee,[11] and others,[12, 13] the anatomy and physiology of the arterial system of the uterus are well known. The venous system is less well understood. As pointed out by Reynolds,[14] menstruation may occur as a series of localized hemorrhages with blood escaping in any of several different ways. It may occur as diapedesis, as direct escape from capillaries or arterioles, or as venous hemorrhages. Of these, 22 per cent of hemorrhages observed by Markee[11] in the monkey were venous. He noted that they lasted on an average for forty-seven minutes in contrast to the other types of bleeding which lasted only a few minutes. From the appearance of the extensive venous lakes in the subepithelial portion of the uterine mucosa, it has been assumed that venous pressure in these structures is relatively high, according to Reynolds.[14] As pointed out by Daron,[10] the free communication of the uteroovarian venous system with the endometrium was first demonstrated by Sampson in 1911 in his study on the circulation of uterine myomas. Daron mentioned the difficulty encountered by Sampson in obtaining a good injection pattern of the arterial system of the endometrium. However, upon injection of the uterine vein, the injection mass was clearly demonstrated in the mucous membrane. In fact, it was this technical difficulty which delayed the study of the endometrial arterial pattern until Daron's work in 1936. Daron clearly demonstrated large endometrial veins opening directly into the lumen of the uterus in the menstruating endometrium of the *Macacus rhesus*. This evidence pointedly suggests that pressure in the uteroovarian venous system is directly transmitted to the veins of the endometrium. It would appear that venous pressure in the ovarian veins is intimately associated with basic endometrial physiology.

Aim of this Investigation

The ovarian vein pressure observations herein reported are aimed at answering the following questions:

1. What is the normal ovarian vein pressure?
2. What is the difference, if any, between the pressure carried in the left ovarian as compared to that carried in the right ovarian vein?
3. Is there evidence of an efficiently performing system of valves in the ovarian veins?
4. How does ovarian vein pressure react to hydrostatic changes?
5. How does the ovarian venous system adapt itself to the increased demands placed upon it by the state of pregnancy?

Normal Ovarian Vein Pressure.—

The mean average of 47 observations of ovarian vein pressure recorded with the zero position of the manometer at ovarian vein level was 14.62 cm. of water (Table I). Considerable variation in individual readings was encountered such as have been observed in studies on peripheral venous pressure. Because the ovarian vein level with the patient in the horizontal position closely approximates the level of the right auricle (8 to 12 cm. from the skin of the back) as determined by Lyons, Kennedy, and Burwell,[5] the ovarian vein pressures can be compared to peripheral venous pressure studies performed by others. According to Landis and Hortenstein,[9] normal venous pressure in the antecubital veins ranges from 5 to 15 cm. of water. The ovarian vein pressure average falls in the upper limits of normal for peripheral venous pressure. It is possible that excitement and increased breathing associated with administration of the anesthetic influenced the venous pressure to rise. Such effort has been shown to produce such changes in peripheral pressure. Landis and Hortenstine mention Brown,[9] who showed that the Valsalva maneuver caused an elevation of peripheral venous pressure of from 9 to 19 cm. of water for periods of thirty minutes. It is possible that ovarian vein average pressure in the unanesthetized, horizontal patient more closely approaches average peripheral venous pressure.

One of the motivating objects of this study was to determine how ovarian vein pressure responded to strain efforts such as can be observed in peripheral venous pressure. In this study it was simple to demonstrate the sensitivity of the ovarian vein pressure to strain efforts. In patient No. 20, straining deliberately induced by the anesthetist resulted in an elevation in venous pressure from 15.4 cm. of water to 34 centimeters. McLennan[6] noticed marked lability of femoral venous pressures continuously recorded during cesarean section performed under local anesthesia. Rises in pressure coincided with maternal straining. More recently Palmer and Walker[15] noticed elevations in right auricular pressure recorded during pregnancy that coincided with painless contractions of the uterus. The magnitude of these variations was from 4 to 10 cm. of water, the pressure rising as the uterus contracted and falling as it relaxed. Muscular activity of any type, therefore, causes elevations in central venous pressure as well as elevations in ovarian vein pressure. With evidence that such influences are directly transmitted to the veins of the endometrium, this information acquires significance both in normal and abnormal uterine bleeding. The benefit of bed rest for patients suffering from uterine bleeding is well recognized. From the standpoint of the ovarian veins, this form of treatment accomplishes two things. The supine position relieves the ovarian veins of the increased influences of hydrostatic pressure and the lessened activity results in a diminution of general venous pressure. These studies suggest that raising the foot of the bed would bring about additional benefit.

Comparison of the Right and Left Ovarian Vein Pressures.—

Anatomical teaching has led to the belief that the pressure carried by the left ovarian vein is elevated over that carried by the right. The oblique junc-

tion of the right ovarian vein with the vena cava is alleged to offer less resistance than the junction of the left ovarian vein with the left renal vein which is accomplished at right angles. Left varicocele in the male and varicose veins of the left broad ligament are explained on this basis.[1] These studies do not substantiate this assumption. In all positions there was no significant difference between the venous pressures in either vein.

TABLE I

CASE	AGE (YR.)	BLOOD PRESSURE	DIAGNOSIS	ANESTHETIC	LEFT OVARIAN VEIN PRESSURE				RIGHT OVARIAN VEIN PRESSURE			
					ZERO*	+15	−15	−20	ZERO	+15	−15	−20
1.	43	110/70	Fibroid	Gen.	12.0	12.2	11.6					
2.	32	120/60	Ovarian cyst	Gen.	9.0	14.0	0.0		9.0	12.6	0.0	
3.	37	110/80	Subinvolution	Gen.	11.0	19.0	5.0					
4.	43	124/80	Ca. cervix	Gen.	19.4	22.8	0.0					
5.	48	116/78	Fibroid	Gen.	17.6	23.0	12.0		16.2	17.0	10.0	
6.	38	140/80	Ovarian cyst, right	Gen.	23.8	27.8	11.0		15.4	17.8	7.0	
7.	49	120/80	Fibroid	Gen.	15.8	19.0	10.9		20.2	39.8	0.0	
8.	47	110/70	Ca. cervix	Gen.	14.2	18.6	7.6		10.8	15.8	5.1	
9.	46	140/86	Fibroids	Gen.	13.0	16.6	9.8		12.2	14.2		
10.	50	150/90	Fibroids	Gen.	11.8	22.0	0.0		12.8	23.8	0.0	
11.	35	110/70	Subinvolution	Gen.	7.0	9.0	0.0		16.8	18.0	0.0	
12.	26	116/80	Ovarian cyst, left	Gen.					21.7	25.2	11.7	
13.	44	120/70	Fibroids	Gen.	17.6	19.0	8.0		27.2	36.0	18.0	
14.	16	100/70	Congestive heart disease Chronic cyanosis Pregnancy 14 weeks	Gen.	17.0	23.0	7.5					
15.	46	115/80	Adenomyosis	Gen.					9.0	16.2	4.0	0.0
16.	44	220/120	Fibroid, carotid aneurysm	Gen.	19.0	21.2	4.0	10.0	10.0	21.2	4.0	10.0
17.	44	120/80	Fibroid	Gen.	19.0	25.4	9.0	7.0	12.2	17.0	7.5	5.0
18.	39	150/90	Adenomyosis	Gen.	10.2	14.0	7.2	5.4				
19.	26	150/95	Diabetes, pregnancy 37 weeks	Spin.	10.0	10.0	5.0					
20.	45	120/70	Fibroid	Gen.	15.4	19.0	10.8		15.4	19.4	18.4	12.4
21.	40	140/100	Fibroid	Gen.	14.6	18.8	10.2	9.2	15.8	22.4	12.2	12.2
22.	43	105/60	Fibroid	Gen.	14.8	21.4	11.6	10.4	13.4	21.4	12.2	10.0
23.	61	130/90	Fibroid	Gen.	20.2	26.2	14.6					
24.	45	125/80	Fibroid	Gen.	11.0	12.4	6.6	7.4	10.4	15.6	4.0	
25.	67	140/80	Ca. fundus; cardiac decompensation	Gen.	12.2	15.8	5.8	8.0	9.2	14.2	6.6	6.8
26.	42	105/70	Fibroid	Gen.	19.0	22.8	14.6	14.6	13.2	17.8	11.6	10.8
27.	37	120/70	Fibroid	Gen.	15.6	19.4	12.8	11.4	13.2	17.2	11.0	9.0
28.	49	130/80	Fibroid	Gen.	12.6	21.6	7.6	8.4	19.2	24.2	15.2	18.0
29.	32	130/70	Pregnancy 40 weeks	Spin.	14.0	17.2	12.0					
30.	44	150/90	Fibroid	Gen.	15.4	20.0	15.2	13.8				
31.	26	120/70	Dermoid cyst, left	Gen.					14.4	24.4	11.8	13.0
Average mean pressure					14.55	19.18	8.13	9.12	14.71	20.24	8.25	10.11

*Zero = horizontal position.
+15 = operating table slanted head upward 15 degrees.
-15 = operating table slanted head downward 15 degrees.
-20 = operating table slanted head downward 20 degrees.

Evidence of Efficient Valves.—

In this study, through alterations in hydrostatic pressure, it was hoped to demonstrate the presence or absence of effective valves in the ovarian veins.

Anatomical controversy as to whether or not valves are present in the ovarian veins has occupied the attention of many. Gray's *Anatomy* states that valves are occasionally found in the ovarian veins. Fagarsanu,[1] basing conclusions on dissection of thirty cadavers, admitted the possibility of anatomical presence of valves but stated that they were probably incapable of resisting the reflux of blood.

These studies support the contention of Fagarsanu. In all except four veins, there was a prompt and significant rise in venous pressure when the table was slanted head upward 15 degrees. A suggestion of valvular action was noted in two patients when a rise in venous pressure occurred in one vein but not the other. A significant rise in ovarian vein pressure failed to develop in the right vein of patient No. 5 and in the left vein of patient No. 24.

Another observation suggesting the absence of valvular action was evident from the respiratory influences transmitted to the water column in the manometer. Respiratory influences were equally apparent with patients in all positions. The impression is gained from these observations that the full effect of hydrostatic pressure must be supported by the ovarian vein wall itself. The ovarian veins lack the support of strong fascia and skin afforded the peripheral veins. The occasional rupture of the ovarian veins is to be expected.

Reaction to Hydrostatic Pressure.—

These studies indicate that the reaction of ovarian vein pressure to increased, as well as decreased, hydrostatic pressure is prompt and considerable. Gynecological surgeons have long recognized how promptly the ovarian veins empty when patients are placed in the Trendelenburg position. In the Henry Ford Hospital the average tilt of the operating table when pelvic surgery is performed is 20 degrees. It has been evident at times that anesthetists have difficulty with patients in this position. Because of this, ovarian vein pressure observations were conducted on 11 patients in this position. It was somewhat disconcerting to find the average ovarian vein pressure in this position higher than when patients were tilted less steeply in the 15 degree position. In the 20 degree position, 12 veins demonstrated a further fall in pressure; in 2 veins the pressure remained unchanged, while in 7 veins the ovarian vein pressure was elevated.

Two patients suffering from major circulatory system disturbances suggested that this paradoxical rise in ovarian vein pressure in the 20 degree position was due to central influences. Patient No. 16 had a large carotid aneurysm. She demonstrated no distress when depressed to the 15 degree head downward position where the left ovarian vein pressure was observed to be 4.0 cm. of water pressure. In the 20 degree position, the patient demonstrated obvious distress and the vein pressure rose promptly to 10 cm. of water. The anesthetist refused to leave the patient in this position and her condition improved when the operating table was leveled. Patient No. 25 was suffering from severe arteriosclerotic heart disease and demonstrated auricular fibrillation at the time of operation. Evident distress associated with elevation in venous pressure occurred when she was placed in the 20 degree position.

Such observations give support to the anesthetist's concern when patients are placed in the steep Trendelenburg position. Because some apparently normal patients demonstrate this reaction when placed in the 20 degree position, gynecologists should give more consideration to this problem when performing pelvic surgery.

Ovarian Vein Pressure During Pregnancy.—

Venous pressure in the peripheral veins during pregnancy has attracted considerable attention. Burwell and McLennan demonstrated a progressive increase in femoral vein pressure during gestation. Similar studies in the antecubital veins showed essentially no change as the result of pregnancy.

Palmer and Walker[15] and Hamilton[16] demonstrated elevations in the right auricular pressure during pregnancy. The pressure in the right auricle showed the highest mean during the third month, after which it slowly fell to normal in the ninth and tenth lunar months. Elevations coinciding with uterine contractions were noted by Palmer and Walker.

Fig. 2.—Photograph showing dilatation of ovarian veins of left ovarian plexus associated with term pregnancy. Picture was taken immediately before delivery of infant.

Fig. 3.—Photograph showing collapse of veins of left ovarian plexus following delivery of infant. This picture was taken immediately after delivery of infant. Same patient as in Fig. 2.

In this study observations during pregnancy were too few to warrant conclusions because only 3 patients were studied. One patient was 14 weeks pregnant and her ovarian vein pressure in the horizontal position was 17 cm. of water. Another patient, a diabetic, operated upon during the thirty-seventh week of pregnancy, had a left ovarian vein pressure in the horizontal position of 10 cm. of water. The third patient was operated upon during the fortieth week of pregnancy. Her left ovarian vein pressure in the horizontal position was 14 cm. of water.

The state of pregnancy induced a remarkable change in the capacity of the ovarian veins (Figs. 2 and 3). This change has been observed by others and the suggestion has been made that the ovarian veins serve as a reservoir for blood during late pregnancy.[15] Upon delivery of the infant, the hyperdistended ovarian veins empty themselves completely. Such evidence demonstrates how the ovarian veins can accommodate an increased blood load without showing an elevation in venous pressure. Investigation under way at present concerns microscopic examination of excised vein segments at the time of cesarean section. Although this part of the investigation is incomplete, it would appear that the vein accommodates for the increased demands placed upon it by pregnancy through simple hypertrophy.

Summary

In this study, 165 ovarian vein pressure observations were performed on 31 patients at the operating table prior to pelvic surgery. The mean average for the group with patients in the horizontal position was 14.62 cm. of water pressure. When this figure was compared to the normal range for peripheral venous pressure, it was found to fall in the higher level of normal. When the pressure carried in the right ovarian vein was compared to that carried in the left ovarian vein, no significant statistical difference was observed. This evidence does not confirm the opinion of anatomists that excessively dilated veins frequently found on the left in both sexes are caused by left gonadal hyperpressure. These ovarian vein pressure studies demonstrated a sharp response to hydrostatic changes. There was practically no evidence suggesting the presence of efficient valves in the ovarian venous system. These features strongly suggest that the pressure carried by the ovarian vein must be supported by the strength of the vein wall itself. Furthermore, from studies done by others, the impression is gained that ovarian vein pressure is directly transmitted to the veins of the endometrium. Studies done with patients placed in the 20 degree modified Trendelenburg position indicated that this position caused distress in some patients. The concern expressed by anesthetists when patients are placed in this position is objectively subtantiated by these observations. In this study there was no evidence that ovarian vein pressure was increased during pregnancy.

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HISTOPATHOLOGICAL CHANGES IN THE CERVIX ASSOCIATED WITH HYPERPLASIA OF ENDOMETRIUM

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A CONTROVERSY has arisen with regard to the etiological role played by excessive estrogens in the production of carcinoma of the cervix. Ayre[1] has reported some observations which have led him to believe that estrogens in excess being picked up and held by a chronically infected and inflamed cervix play an important part in producing abnormal cornification of cervical squamous mucosa and indeed may play some part in producing carcinoma of the cervix. It is his impression, supported by many animal experiments by other investigators, that estrogens are detoxified in the liver. If the dietary supply of thiamin or riboflavin is deficient, the liver fails in its function of detoxification and the blood estrogen level is elevated. Estrogen is trapped and held in the inflamed tissues of the infected cystic or eroded cervix and the squamous mucosa reacts to the estrogen by showing increased proliferative activity. The superficial cells became cornified in abnormally large numbers and are cast off, allowing the investigator, as Ayre[1] has pointed out, to estimate roughly the amount of estrogen activity by counting the cornified epithelial cells in a cervical or vaginal smear.

That excessive estrogens play any role in the pathogenesis of cervical carcinoma is refuted by Greene and Suckow.[2] To support their belief they have shown that in eleven patients with carcinoma of the cervix there was only one with hyperplasia of the endometrium. Still more weight is given to their thesis by the results of Martzloff[3] and Pund and Auerbach.[4] In these larger series carcinoma of the cervix was associated with hyperplasia of the endometrium in only 2.4 per cent and 5 per cent, respectively. The results of such reviews, however, seem of questionable value, without first having a control series and, second, without establishing certain criteria for the microscopic diagnosis of hyperplasia of the endometrium.

We proposed, in view of this controversy, to review the gynecopathological material in the Ottawa Civic Hospital. Besides examining endometria from cases of histologically diagnosed carcinoma of the cervix we examined also endometria from cases in which there had been a diagnosis of hyperkeratosis of the cervix and/or squamous metaplasia of cervical mucosa. These two conditions were included in this review because they have been considered by some as precursors of squamous-cell carcinoma of the cervix. Whether or not this is so, they represent, at least, an abnormal cornification of cervical mucosa.

Material

The material for this review includes surgical specimens examined in the five-year interval, from 1945 to 1949, inclusive. In order to obtain the series

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of twenty-six cases of carcinoma of the cervix with corresponding available endometria, the material from a ten-year period, ending in 1949, had to be examined. Two control series have been used, one showing the incidence of hyperkeratosis and metaplasia of the cervix associated with hyperplasia of endometrium and the other showing the incidence of these changes where the endometrium was normal, whether proliferative, secretory or menstrual.

Fig. 1.—Adenomatous hyperplasia of endometrium with infolding of the glandular epithelium. This may be the result of hyperplasia of both the epithelial and stromal elements. Ballooning of the glands is prevented by the density of the stroma so that the lining is forced to invaginate. (×80.)

Criteria for the diagnosis of endometrial hyperplasia vary with different pathologists and to make the problem more intricate several different types of hyperplasia are recognized and described. Hertig and Sommers[5] described focal and generalized hyperplasia. In the first they included endometrial polyps and the focal infolding of endometrial gland lining; in the second, cystic and adenomatous hyperplasia. In this review we have rejected focal types of hyperplasia, though we have included those endometria in which multiple polyps resulted from a generalized exuberant growth of endometrium as well as those exhibiting epithelial infolding of many of the glands as part of a generalized adenomatous hyperplasia (Fig. 1). We have also included one type of endometrial hyperplasia left undescribed by Hertig and Sommers. It is considered a real hyperplasia, though the Swiss-cheese appearance is lacking microscopically and there is no true adenomatous proliferation of glands extending through the endometrium. In this type the superficial glands are few in number and widely separated by a copious stroma. On the appearance of the superficial layer alone it could be considered stromal hyperplasia. Grossly, the endometrium is too thickened even for one in the secretory or premenstrual phase. On the slide, following shrinkage from fixation and dehydration it still measures 0.5 to 0.6 cm. in depth. In the basal glands, which appear to react more readily to whatever stimulus produces hyperplasia, there is increased activity. Mitotic figures are scattered about in large numbers, within both the stroma and the glandular epithelium. The epithelial cells lining the glands are crowded and heaped-up into several layers instead of being arranged in a pseudostratified layer; the gland spaces while not cystic are larger than normal glands in the basal layer and are branching instead of tubular (Fig. 2).

Only infiltrative carcinomas of the cervix were included in this study. Carcinomas in situ being eliminated as borderline.

Cases of metaplasia of the cervix likewise were embraced in this series, only if they were clear-cut. Those cases were not included in which there was merely an ascent of the squamous epithelium into the cervical canal so that it covered or surrounded the mouths of cervical glands, nor were those cases in which the squamous epithelium climbed for a short distance up the necks of cervical glands. Moreover, before a diagnosis of squamous metaplasia of the glandular epithelium was made, intercellular protoplasmic bridges were demonstrated.

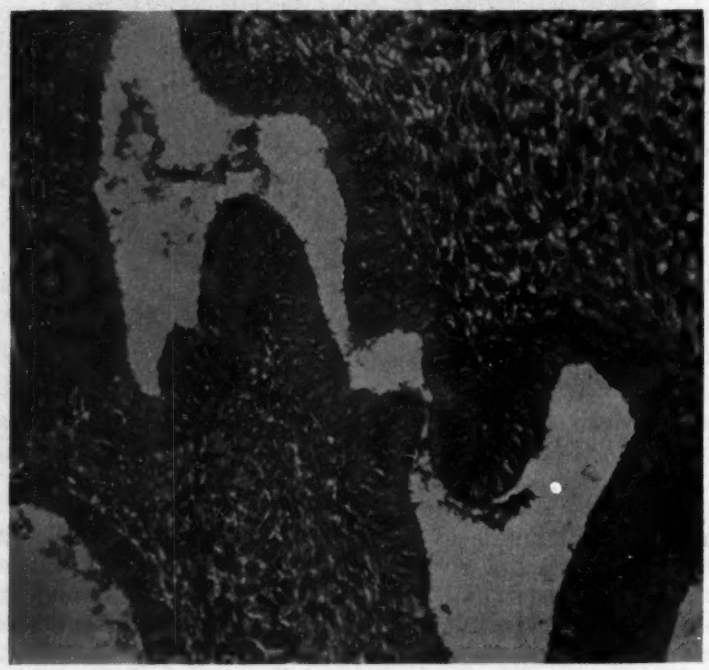

Fig. 2.—Branching glands in basal endometrium where more superficially there were neither cystic nor adenomatous changes in the glands but where the endometrium was very much thicker than normal. The glands spiraled up for 5 or 6 mm. in a section of tissue that had undergone shrinkage owing to fixation and dehydration. The endometrium was of a nonsecretory type. Note mitotic figures within both stromal and epithelial cells. (×160.)

The term hyperkeratosis is used in this report to include cases of both parakeratosis and true hyperkeratosis as defined by Schiller.[6] We have purposely avoided the term leucokeratosis favored by Schiller because he described in his thesis the gross appearance of such lesions, while we are primarily interested in the microscopic picture. In the diagnosis of hyperkeratosis a search was made for certain features. The most important was a thickened layer of squamous mucosa with the production of either a keratohyalin layer (keratosis) or several layers of degenerating squamous cells still retaining their nuclei (parakeratosis). A list of other characteristics exhibited in cervices with hyperkeratosis would include hyperactivity of the basal layers of cells with increased numbers of mitotic figures and some loss of polarity of the cells; increased vascularity of fibrous stroma immediately below the squamous epithelium with the appearance of a few capillaries in the mucosa; a wavy contour of the basal aspect of the epithelium frequently resembling the rete pegs in the skin; and, finally, the appearance of chronic inflammatory cells in the stroma and contiguous to the basal cells.

Results

The results have been assembled in Table I. It will be noted that in 26 cases of carcinoma of the cervix, 13, or 50 per cent, had an associated hyperplasia of the endometrium while nine had a normal endometrium. The remaining 4 cases were in postmenopausal women and senile atrophy left no trace of the picture that had existed in the endometrium before the cessation of menses. If these 4 cases are omitted, carcinoma of the cervix would be associated with hyperplasia of the endometrium in 59 per cent of the 22 cases and with a normal endometrium in 41 per cent.

TABLE I

CERVIX	TOTAL NO. CASES IN WHICH ENDOMETRIUM AVAILABLE	ATROPHY OF ENDOMETRIUM	NORMAL PREMENOPAUSAL ENDOMETRIUM				HYPERPLASIA OF ENDOMETRIUM	
			PROLIF.	DIFFERENTIAL	TOTAL NO.	TOTAL %	NO.	%
Carcinoma	26	4	6	3	9	35	13	50
Metaplasia	56	16	11	4	15	26.8	25	44.8
Hyperkeratosis	84	32	20	7	27	32.1	25	29.3

Whether or not one is justified in omitting the 4 cases with atrophy of the endometrium may be questioned. The very fact that some cases showed atrophy of the endometrium while the cervix was undergoing a carcinomatous change may be used in the argument that hyperestrinism played no role in the pathogenesis of cervical carcinoma. Such was the argument of Greene and Suckow.[2] It needs to be remembered, however, that carcinoma may appear many years after the initiating stimulus has ceased. Hence, Hertig and Sommers[5] were able to report a lapse of ten to thirteen years between the time hyperplasia of the endometrium was first diagnosed and the diagnosis of adenocarcinoma of the fundus, while Younge, Hertig and Armstrong[7] found the latent period between the occurrence of cervical carcinoma in situ and clinically evident carcinoma to be nine years.

The incidence of associated metaplasia of the cervix and endometrial hyperplasia is less striking at first sight, but again by omitting the cases of atrophy of the uterus we find that the association existed in twenty-five, or 62.5 per cent, of 40 cases, while metaplasia was associated with a normal endometrium in only 15, or 37.5 per cent of cases.

TABLE II

CERVIX	NORMAL ENDOMETRIUM	HYPERPLASIA OF ENDOMETRIUM		
		CYSTIC	ADENOMATOUS	TOTAL
	77 CASES	127 CASES	43 CASES	170 CASES
Hyperkeratosis	10.4% (8 cases)	11% (14 cases)	2.3% (1 case)	8.8% (15 cases)
Parakeratosis	28.6% (21 cases)	44.1% (56 cases)	46% (20 cases)	44.7% (76 cases)
Metaplasia	6.5% (5 cases)	26.8% (34 cases)	23.3% (10 cases)	25.9% (44 cases)
Reduplication of endocervical epithelial cells	13% (10 cases)	38.6% (49 cases)	30.2% (13 cases)	36.5% (62 cases)
Increased glycogenation of squamous cells	33.8% (26 cases)	63% (80 cases)	69.8% (30 cases)	64.7% (110 cases)

Similarly hyperkeratosis of the cervix was associated with endometrial hyperplasia in 25, or 48 per cent, of 52 premenopausal women while it was associated with normal endometrium in 52 per cent of cases.

To get a proper control series for this study all uteri removed in this hospital during the five-year interval between 1945 to 1949 were studied. There were well over 1,000. Only those were used, however, in which sections from the cervix showed adequately the squamous epithelium of the vaginal aspect and the glandular mucosal lining of the cervical canal, while sections from the fundus showed a wide band of lining endometrium attached to the musculature, not distorted by curettement, antiseptic, fibroids, etc. within the uterus. All other cases excluded, 247 remained acceptable. Unavoidably, some of those cases used in Table I have been included in the control series. It was found, however, that there were many cases in which metaplasia and hyperkeratosis of the cervix had not been indexed as such and these were not included in Table I. One weak link must be pointed out. Serial sections of the cervices were not taken. The material available consisted of routine surgical sections. We believe, nevertheless, that the series is large enough to make up for this defect. The only available cases of carcinoma of the cervix in which endometria were at hand had been included in Table I so that no control series could be devised for these.

In the study of the cervices such features were considered as cystic changes in the cervical glands, erosion, inflammation, extension of squamous epithelium into the endocervical canal, basal cellular activity, rete peg formation, glycogenation of squamous cells and reduplication of cells beneath the columnar epithelium of the endocervix and its glands. One or two of these features appeared to have a higher incidence when associated with hyperplasia of the endometrium. The findings are reported in Table II. Hyperkeratosis of the control series has been divided into parakeratosis and true hyperkeratosis where a keratohyalin layer covered the vaginal surface. Hyperplasia of the endometrium has been classified as cystic and adenomatous.

The incidence of the various changes in the cervix associated with cystic hyperplasia and the incidence of these changes associated with adenomatous hyperplasia are reasonably comparable, except in the case of hyperkeratosis. The incidence of parakeratosis, metaplasia, reduplication of endocervical epithelial cells, and increased glycogenation of squamous cells is higher, associated with hyperplasia of the endometrium, whether cystic or adenomatous, than when associated with normal endometrium. The development of the keratohyalin layer superimposed on the squamous epithelium of the cervix appears to result from physical changes, such as the friction and drying suffered by the cervix in procidentia. The other changes seem, however, to depend upon physiological stimuli.

The most striking disparity in the incidence of cervical changes associated with normal and hyperplastic endometria is in connection with the squamous metaplasia of the cervix and reduplication of endocervical epithelial cells. The latter needs some explanation. In the zone of unrest at the point of transition between squamous and columnar epithelium where lymphocytes are present at all times and where carcinoma of the cervix begins, we frequently found the reduplication of cells. Below the columnar epithelial lining of the cervical canal and its glands there occurred a layer of cells similar in appearance to the basal cells of epidermis (Figs. 3 and 4). Mitotic figures were present among these basal cells. Their proliferation soon resulted in several layers of pavementlike cells, displacing the columnar epithelium outward (Fig. 5). This stratified epithelium has been observed to lose the superficial layer of columnar cells and develop intercellular protoplasmic bridges; to become, in other words, true squamous metaplastic epithelium.

Fig. 3.—Reduplication of cells in the lining of the endocervical canal. Note the number of mitotic figures in the basal layer of cells. (×160.)

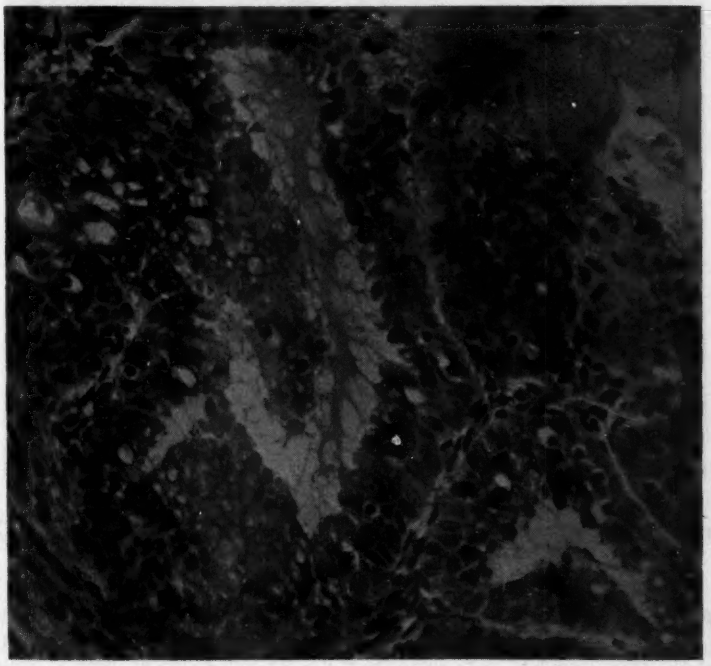

Fig. 4.—Reduplication of cells lining cervical glands. This is considered a stage in the pathogenesis of squamous metaplasia. (×160.)

Comment

As compared to the observations of Auerbach and Pund[8] who found metaplasia in 63.5 to 85.0 per cent of cervices, the incidence of metaplasia in our material is low. Failure to section each cervix serially is undoubtedly responsible. Auerbach and Pund[8] have pointed out that the increasing incidence of squamous metaplasia of the cervix with increasing age "roughly parallels the curve of declining ovarian activity with relative hyperestrinism." The increased incidence of squamous metaplasia of the cervix with endometrial hyperplasia supports the argument that hyperestrinism partakes in the pathogenesis of squamous metaplasia. Furthermore, metaplasia of the cervix has occurred following long-continued administration of an estrogen to mice past the reproductive period.[9] Similar changes appeared in rats subjected to hyperestrinism[10] and, indeed, squamous metaplasia of the cervix was produced by Wollner[11] in an oophorectomized woman by prolonged estrone administration. After discontinuance of the hormone therapy there was a disappearance of the metaplastic growths. That estrogen may stimulate the production of the squamous metaplasia has been further substantiated by the observation in this laboratory of squamous metaplasia in prostatic glands following stilbestrol therapy for carcinoma of the prostate.[12]

Fig. 5.—Early metaplasia of cervical glands. Note the columnar epithelium becoming displaced by the underlying squamous epithelium. In this there is no glycogenation of cells. (×80.)

Engorgement of the mammary gland in the newborn is considered a manifestation of stimulation by the maternal endocrines. Why would there not be changes within the cervices of neonatal female infants? The uteri in several newborn infants that had come to autopsy were examined. In the endocervical canal of about half of these there was reduplication of cells lining the canal and its glands (Fig. 6). As a result of too weak or too brief a stimulation

Fig. 6.

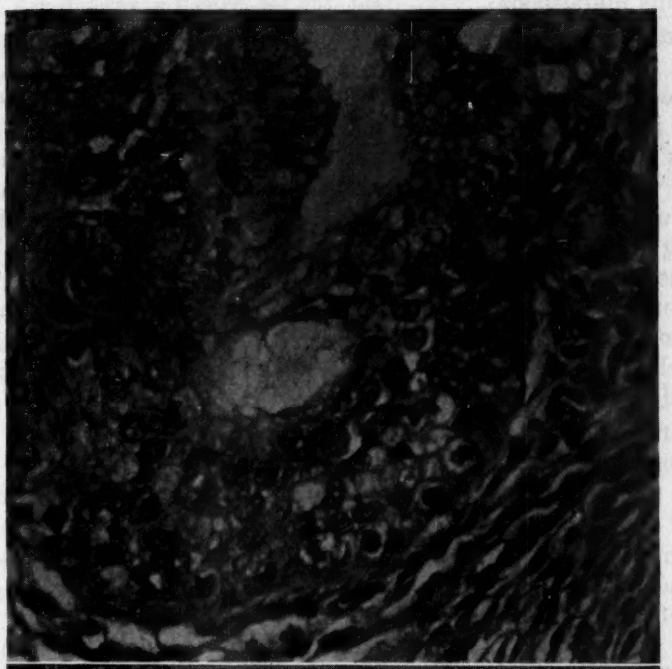

Fig. 7.

Fig. 6.—The cervical gland of a newborn female infant. There is reduplication of the lining epithelium. (×320.)

Fig. 7.—Marked thickening and increased glycogenation of squamous epithelium clothing the vaginal aspect of the cervix in a newborn infant. (×80.)

or as a result of unresponsiveness of the cells this change had not proceeded to a squamous metaplasia.

A finding that was constant, however, in the cervices of newborn female infants was thickening of the squamous mucosa of the vaginal aspects and marked glycogenation of these cells (Fig. 7). This brings us to the findings as recorded in Table II, that increased glycogenation of the squamous epithelium occurs twice as frequently when associated with hyperplastic endometrium as when associated with normal endometrium. A study by Davis and Pearl[13] of the changes in the vaginal mucosa during pregnancy has shown a thickening and increased glycogenation of the cells. These changes have also been described in the cervix,[14] and in several gravid uteri studied in this laboratory the same changes have been noted in the squamous epithelium. In the case of the vagina the increased estrogen secretion has been accredited with these changes, while in the case of the cervix it is said to be a combined estrogen and progesterone effect.

The parakeratosis seems to be the result of increased activity and thickening of the squamous mucosa. This nucleated layer of degenerating cells is more or less a normal component of the thickened epithelium.

Novak[15] has described the changes occurring in the endocervical mucosa during pregnancy. Some of these changes have also been noted in cervices when the endometrium was hyperplastic, though to a somewhat lesser degree. Branching and proliferation of the cervical glands approaching an adenomatous growth was the most striking change. It seemed that the incidence of cystic glands was no higher than in association with a normal endometrium.

Now there comes a discrepancy in our observations. We have noted a higher incidence of carcinoma associated with hyperplasia of the endometrium and also that there is increased glycogenation of the squamous cells. Even in metaplastic growths it is common to see glycogenation of the cells. One of the characteristics of carcinomatous areas of the cervix is the *lack* of cellular glycogenation. Hence Schiller's iodine test causes the cervical mucosa to turn purple, except in the areas of malignancy where the cells are without glycogen.

We have seen in the cervical canal reduplication or benign proliferation of cells and even squamous metaplasia in which there was failure of glycogenation. It seems then that there must be a factor added to hyperestrinism which stimulates malignant proliferation of epithelial cells. The presence of this unknown factor should be considered where the proliferating cells in the endocervical mucosa fail to follow the course whereby they developed into well-glycogenated squamous epithelium, but instead continue to proliferate remaining basophilic, in the hematoxylin and eosin stained sections, and immature (Fig. 5).

Hyperplasia of the endometrium may also be considered an alert signal for carcinoma of the cervix as it has become for fundal carcinoma.

Conclusions

1. Carcinoma and squamous metaplasia of the cervix are more commonly associated with hyperplastic than with normal endometria.

2. These changes are believed to be the effect of hyperestrinism.

3. Some other factor, the nature of which is as yet unknown, is necessary for the development of carcinoma.

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ANALYSIS OF DEATHS OCCURRING IN 5,318 GYNECOLOGIC OPERATIONS

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IN 1932 the senior author published an analysis of 6,022 operations which were performed on the Gynecologic Service at the Cook County Hospital between Jan. 1, 1926, and Jan. 1, 1931. During the following years, important advances were made in medicine and with them, new concepts arose in the management of gynecologic patients. The discovery of the sulfonamides, penicillin, and streptomycin radically changed the therapy of pelvic infections and the indications for their surgical treatment. The development of the blood bank at the Cook County Hospital made an adequate supply of blood available twenty-four hours a day. The practice of absolute bedrest for several days after operation gave way to early ambulation with a decrease in the incidence of some of the more serious postoperative complications. New and better operative techniques and improved methods of anesthesia were introduced. The development of the Wangensteen, Levine, and Miller-Abbott tubes and the use of vitamins and amino acids helped to improve the results of gynecologic surgery. Finally, and of considerable importance at the Cook County Hospital, was the reorganization of the Department of Gynecology. At the time of the first study (1926-1930), the Staff was composed of five attending physicians with two available alternates. For each of the two services there was a senior intern who had already served one year of an eighteen months' internship and a junior intern who was serving the first six months of a similar service. There were no residents. In 1932 the attending staff was increased to eight and each attending gynecologist was allowed to select an associate. The first resident was assigned to the department in 1941 but during the war years the shortage of interns and residents left the department undermanned. However, in 1946, an intensive program of resident training was inaugurated and the number of residents was increased to four.

In view of the many important advances made during the last two decades, we decided to review again the operative mortality on the gynecologic service. The five-year period from 1943 through 1947 was used as a basis for the present study.

Material

A total of 5,318 operations was performed by the gynecologic staff of the Cook County Hospital during the five years ending in 1947. Of the 5,318 operations, 4,391 were major and 927 were minor operations. During these five years, there were 69 operative and postoperative deaths up to three months

after surgery. The uncorrected mortality was 1.3 per cent. The number of operations and deaths for each year is shown in Table I. The highest mortality for any one year occurred in 1943 when there were 23 deaths among 1,064 operations yielding a mortality of 2.16 per cent. The lowest mortality in any one year occurred in both 1946 and 1947 with eight deaths for each year, the rates being 0.7 and 0.67 per cent, respectively.

Table I shows a comparison between the mortality rate from 1926 through 1930, hereafter referred to as the first period or series, and the death rate from 1943 through 1947, hereafter referred to as the second period or series. In the first period there were 6,022 operations, of which 88 per cent were major and 12 per cent were minor procedures. During the second period, there were 5,318 operations, of which 83 per cent were major and 17 per cent minor. The number of operative and postoperative deaths showed a pronounced decline, from 213 deaths representing a mortality rate of 3.5 per cent in the first series, to 69 deaths representing a mortality rate of 1.3 per cent for the second series.

TABLE I. OPERATIVE MORTALITY, 1943-1947

YEAR	NO. OF MAJOR OPERATIONS	NO. OF MINOR OPERATIONS	TOTAL NO. OF OPERATIONS	NO. OF DEATHS	MORTALITY RATE (%)
1943	852	212	1,064	23	2.16
1944	794	152	946	14	1.48
1945	848	132	980	16	1.63
1946	930	205	1,135	8	.70
1947	967	226	1,193	8	.67
Total	4,391	927	5,318	69	1.30
1926 to 1930	5,308	714	6,022	213	3.5

Type of Operation Performed

Table II shows the number of each type of operation performed during both periods and their mortality rates.

Analysis reveals a considerable change in the choice of operative procedure after the seventeen-year interval. Although the number of major operations performed in the second series was less than in the first, the number of hysterectomies increased from 2,117 to 3,196. Thus, we are now performing almost one-third more hysterectomies than 17 years ago even though we are doing less major surgery. This can, in part, be explained by the following observation. When the number of salpingo-oophorectomies, salpingectomies, oophorectomies, and defundations for each period are added together, we obtain a total of 1,189 for the first period and only 445 for the second period. The marked decrease in the number of defundations and operations confined to simple removal of the adnexa is therefore in contrast to the rise in the number of hysterectomies performed. Apparently, whenever it was decided to remove the adnexa, the uterus was also extirpated.

The type of hysterectomy performed has also undergone considerable change. Thus, during the first period there were only 551 total hysterectomies while during the second period there were 1,250. This trend toward performing a total hysterectomy rather than a supravaginal hysterectomy is even more striking if the figures for the second period are analyzed. We find that each year there was a decline in the number of supravaginal hysterectomies with a corresponding increase in the number of total hysterectomies.

TABLE II. MORTALITY FOR THE DIFFERENT OPERATIONS PERFORMED

TYPE OF OPERATION	NUMBER 1926-30	NUMBER 1943-47	DEATHS 1926-30	DEATHS 1943-47	MORTALITY 1926-30 (%)	MORTALITY 1943-47 (%)
Abdominal supravaginal hysterectomy	747	245	6	3	0.8	1.2
Abdominal supravaginal hysterectomy with removal of part or all of the adnexa and/or appendix	661	1,170	59	13	8.9	1.1
Abdominal total hysterectomy	201	217	11	3	5.5	1.4
Abdominal total hysterectomy with removal of part or all of the adnexa	350	1,033	15	11	4.3	1.06
Vaginal hysterectomy	158	531	3	4	1.9	0.75
Vaginal plastic	329	136	4	0	1.2	0.0
Salpingo-oophorectomy	281	231	7	3	2.5	1.3
Oophorectomy	115	72	4	2	3.5	2.8
Salpingectomy	344	27	6	1	1.7	3.7
Exploratory laparotomy	133	62	7	10	5.3	16.0
Defundation	449	115	18	0	4.0	0.0
Colpotomy	89	125	8	6	9.0	4.8
Myomectomy, abdominal or vaginal	53	54	3	1	5.7	1.8
Suspension of uterus	535	60	4	0	0.7	0.0
Appendectomy	123	21	3	0	2.4	0.0
Trachelorrhaphy or amputation of the cervix	76	30	2	0	2.6	0.0
Biopsy	31	81	12	1	38.7	1.2
Vulvectomy	13	10	2	1	15.4	10.0
Vesicovaginal fistula	7	22	1	0	14.3	0.0
Colpocentesis		34	0	3	0.0	8.8
Curettage		442	2	1		0.22
Le Fort operation		13		1		7.7
Iliac artery ligation		8		1		12.5
Paracentesis	2			1		
Supravaginal amputation of inverted uterus		1		1		100.0
Miscellaneous	2		27			
Colostomy	14		11		78.6	
Watkins-Wertheim interpositions	21	0	0	0	0	0
Radium insertion		294		2		0.68

The frequency and type of vaginal surgery have also undergone considerable change since the first study was made. During the first period there were 329 vaginal plastic operations and this number decreased to 136 during the second period. However, in the first period there were only 158 vaginal hysterectomies while during the second period the number rose to 531. Of the 531 vaginal hysterectomies, 336, or about two-thirds, were combined with a plastic operation. There was, therefore, a considerable decrease in the number of patients in whom only a vaginal plastic operation was performed with a much greater tendency to remove the uterus vaginally and to repair the pelvic floor at

the same time. This change in attitude represents a second reason why there was a one-third increase in the number of hysterectomies performed in the two periods studied.

In addition to the trends already discussed, the following comparison should be noted. Salpingectomies decreased from 344 to 27, defundations were reduced from 449 to 115, uterine suspensions dropped from 535 to 60, trachelorrhaphies decreased from 75 to 30, and Watkins-Wertheim interposition operations decreased from 21 to 0. Finally, in the first period there were 14 colostomies following which eleven women died. In the second period the need for such a procedure on the gynecologic service did not arise at all.

Mortality Rates for the Different Operations Performed

In Table II the number of deaths following the different types of operations performed are compared for each five-year period. In general, the mortality rates for the various operative procedures decreased. However, one exception to this rule occurred. When a simple supravaginal hysterectomy was performed, the mortality rate increased from 0.8 per cent for Group One to 1.2 per cent for Group Two. The increased death rate for Group Two can probably be accounted for by the fact that in recent years the conservative operation was usually limited to the technically difficult cases and to patients who were poor operative risks.

When a total hysterectomy alone was performed, the mortality rate showed a decided drop in the second group. There were 11 deaths in the first period and only 3 in the second period. Hence, there was a drop in the mortality rate from 5.5 per cent to 1.4 per cent. An even more impressive change occurred when part or all of the adnexa were removed. During the first period there were 661 supravaginal hysterectomies with removal of part or all of the adnexa as compared to 1,170 for the second period. In spite of the increase in the number of these operations, the deaths decreased from 59 to 13 and the mortality rate decreased from 8.9 per cent to 1.1 per cent. Likewise, when total abdominal hysterectomy was performed with removal of part or all of the adnexa, the number of operations increased from 350 for Group One to 1,033 for Group Two while the fatalities decreased from 15 to 11 and the mortality rate dropped from 4.3 per cent to 1.0 per cent.

In spite of the increased number of vaginal hysterectomies, the mortality rate decreased from 1.9 to 0.75 per cent.

A study of the mortality rates for the various types of hysterectomies performed during the second period reveals that the lowest death rate occurred following vaginal hysterectomy. However, it should be noted that in general this operation was confined to patients having little adnexal disease and a uterus easily movable. When the abdominal approach was utilized, total hysterectomy with removal of part or all of the adnexa actually had a lower mortality than simple supravaginal hysterectomy.

Indications for Surgery in the Fatal Cases

In Table III the indications for surgery in the patients who died are compared for each five-year period. The indications for surgery among those patients who died in the first group were in the following order of frequency: fibromyomas 69 cases, pelvic inflammatory disease 65 cases, and malignancy 31 cases. This is in sharp contract with the second period when malignancy ranked first with 24 cases instead of third as the most frequent indication for surgery. Fibromyomas were second with 22 cases, and inflammatory disease ranked third with 15 cases.

During the first period there were 13 deaths among patients operated on for ovarian cysts, 11 fatalities in patients operated on for intestinal obstruction, and 8 deaths in those operated on for repair of cystocele and rectocele. There were no deaths of patients operated on for these conditions in the recent study.

TABLE III. OPERATIVE DIAGNOSIS OF THE FATAL CASES

DIAGNOSIS	NUMBER 1926-30	PER CENT 1926-30	NUMBER 1943-47	PER CENT. 1943-47
Malignancy	31	15	24	35
Fibromyoma of uterus	69	32	22	32
Acute and chronic salpingitis or pelvic inflammation	65	30	15	22
Functional bleeding			3	4.5
Prolapse	2	0.9	3	4.5
Ectopic pregnancy	1	0.5	1	1.5
Tuberculous peritonitis			1	1.5
Intestinal obstruction	11	5		
Ovarian cyst	13	6		
Cystocele and rectocele	8	4		

Causes of Death Among Patients Undergoing Gynecologic Surgery

1. Sepsis.—In the original analysis, reported by Greenhill, it is stated, "Almost half of all the fatalities (213 cases) were due to peritonitis and ileus and these are listed together because whenever an ileus occurred peritonitis was also present." Thus, in the first period 104 deaths resulted from infection and this represented 48.8 per cent of the 213 deaths. In the second period there was a pronounced reduction in this figure, only 20 patients having died as a result of sepsis. These 20 deaths represented 29 per cent of the fatalities as shown in Table IV. The enormous decrease in the number of patients dying from infection (from 104 to 20) is one of the main factors in the reduction of the operative mortality.

TABLE IV. CAUSE OF DEATH, 1926-1930, COMPARED TO THAT OF PERIOD, 1943-1947

CAUSE OF DEATH	NO. 1926-30	NO. 1943-47	% 1926-30	% 1943-47
Peritonitis and ileus	104	20	48	29
Hemorrhage and shock	35	13	16.4	19
Embolism	18	2	8.5	2.9
Pneumonia and atelectasis	18	4	8.5	5.8
Malignancy and cachexia	16	14	7.5	20
Myocardial failure	12	6	5.2	8.7
Uremia	2		0.9	
Cerebral thrombosis	1	2	0.5	2.9
Acute dilatation of stomach	1		0.5	
Septicemia	1	1	0.5	1.4
Pyelocystitis	1	3	0.5	4.6
Gas gangrene	1		0.5	
Pellagra	1		0.5	
Encephalitis or meningitis	1		0.5	
Pyemia	1		0.5	
Anesthesia		1		1.4
Tuberculosis		1		1.4
Intestinal obstruction		1		1.4
Unknown		1		1.4
Total	213	69		

Not only is it interesting to compare the number of deaths from infection in the two series but also in each of the five years of the second series. A study of Table V reveals that peritonitis as a cause of death showed a precipitate drop

in 1946 and 1947. Thus, during 1943, 1944, and 1945 there was an average of 6 deaths per year from peritonitis but during 1946 and 1947 there was only one death for each year. The sharp decrease in such deaths in the recent series is largely due to the use of penicillin which became available for general distribution at the Cook County Hospital in 1946. Our study shows further that, during the first period, when neither the sulfonamides nor penicillin was available, an average of 21 patients died each year as the result of infection following surgery. This number represented 48.8 per cent of the fatal cases. During 1943, 1944, and 1945, when only the sulfonamides were available to treat peritonitis, the death rate decreased to an average of 6 per year which represented 34 per cent of the fatalities. Finally, in 1946 and 1947, when both penicillin and the sulfonamides were used, the deaths from postoperative peritonitis decreased to one a year which represented only 12.3 per cent of the fatalities for these two years.

TABLE V. CHIEF CAUSES OF DEATH IN OPERATIVE CASES IN 1943-1947 PERIOD

DIAGNOSIS	1943	1944	1945	1946	1947	TOTAL	PER CENT
Peritonitis	7	5	6	1	1	20	29
Malignancy	3	3	1	4	3	14	20
Hemorrhage and shock	6	1	5		1	13	19
Myocardial failure	1		2	1	2	6	8.7
Pulmonary complications	2	1	1			4	5.8

Another factor which undoubtedly had considerable favorable influence in decreasing the mortality from postoperative infection was the more conservative surgical attitude adopted after the advent of the sulfonamides. The beneficial therapeutic response which the majority of patients with active pelvic inflammatory disease showed when the sulfonamides were first used and later when penicillin was introduced made it possible in most instances to postpone surgery until all signs of active infection had subsided. The results of such a policy are self-evident and lead us to re-emphasize the danger of operating in the presence of active pelvic inflammatory disease. We believe that after all signs of active infection have subsided, a minimum of two and preferably three months should elapse before surgery is attempted.

2. Hemorrhage and Shock.—During the first period, 35 patients who underwent surgery died from hemorrhage and shock. However, during the second period only 13 patients died as a result of hemorrhage and shock. We believe two factors are responsible for this evident decrease. The first factor is the blood bank and the liberal use of blood transfusions preoperatively, during operation, and postoperatively. The second and less apparent factor is the better organization of the gynecologic service and particularly the development of the resident training program. This is borne out by the fact that during 1943, 1944, and 1945, when the service was understaffed because of the war, there were 6, 1, and 5 deaths, respectively, from hemorrhage and shock (Table V). In 1946 and 1947 when the present resident program was inaugurated there was but one death for the two years. Thus, although the blood bank was in existence and the attending staff relatively unchanged during the war years and afterward, there was a definite decline in the death rate from hemorrhage and shock. Apparently, because of sufficient residents and interns after the war, there was better preoperative preparation and more experienced postoperative care.

3. Pneumonia and Atelectasis.—Of the 213 deaths in the first series there were 18 resulting from pneumonia and atelectasis which represented 8.5 per cent of the total mortality. Among the 69 deaths in the second series, there

were only 4 fatalities from these pulmonary complications and the mortality rate dropped to 5.8 per cent. Here, too, the decrease was probably due in great part to the use of the sulfonamides and penicillin. What effect early ambulation has had is conjectural. However, during the period of the second study early ambulation was utilized by almost all members of the gynecologic staff and consisted in getting the patient out of bed any time from the day of surgery to the third postoperative day. No set rule was in force, the decision being left to the attending gynecologist and/or his resident.

4. Pulmonary Embolism.—In the first series there were 18 deaths from pulmonary embolism. In a careful examination of the records of the 69 deaths for the second series, only 2 instances of pulmonary embolism could be found and 1 of these did not present a clear-cut picture of such a complication and neither was such a diagnosis made at the time of death. Re-examination of the case record, however, makes such a diagnosis the most likely cause of death.

We believe the decrease in deaths from pulmonary embolism is primarily due to early ambulation postoperatively. In favor of this opinion is the fact that treatment of phlebothrombosis on the gynecologic service has been conservative. There were only isolated instances of vein ligation, and Dicumarol and heparin were not made generally available at the Cook County Hospital until 1946. Consequently, any attempt to explain the reduction in the number of pulmonary emboli in this series of cases to improved methods of treating phlebitis is not justified.

5. Malignancy.—In the first series there were 16 postoperative deaths from malignancy which represented 7.5 per cent of the 213 fatalities. In the second series there were 14 such deaths and they represented 20 per cent of the 69 deaths. The increase in the incidence of deaths from malignancy for the second series is not an actual increase but is due to the decrease in the total number of deaths for the five years.

6. Myocardial Failure.—In the first series there were 12 operative and postoperative deaths from myocardial failure, while in the second series there were but 6 such deaths. Although the number of fatalities for the second series was half the number of the first series, the mortality rate rose from 5.2 to 8.7 per cent. The decrease in the actual number of deaths was in part due to better supervision and to the more frequent consultations with the medical staff whenever a patient gave a history of or showed signs of heart disease.

An analysis of the 6 deaths in the second series reveals that 4 of the patients were seen by a medical consultant. The cardiac status of these few was said to be compatible with surgery but all died of acute heart failure. Three of the 6 patients gave a history of previous cardiac decompensation and of these 3, 2 were seen by a medical consultant and approved for surgery. Two of these 3 women were operated upon because of fibromyomas, but in one an early endometrial carcinoma was also found at the time of laparotomy. The third patient was operated upon without medical consultation for prolapse of the uterus.

These 6 cases lead us to emphasize the dangers of subjecting any patient with a history of previous cardiac decompensation to surgery. Elective operations on such patients should rarely be performed. Even necessary surgery should be done only after consultation with a cardiologist and as much preparation and care as is possible should be given before the operation. In the rare instances where gynecologic surgery is necessary, the anesthetist should be consulted about the type of anesthesia to be used.

Patients with cardiac disease and no evidence of history of decompensation likewise run an increased risk when subjected to surgery and they too, should be given the benefit of medical consultation. However, it must be remembered

that in surgical patients with heart disease, irrespective of a history of previous decompensation, the amount of cardiac reserve is sometimes unpredictable.

Summary

A study was made of the deaths following surgery on the gynecologic service of the Cook County Hospital for the five years from 1943 to 1947 and the results compared with those published from the same hospital in 1932. During the first five-year period, 6,022 gynecologic operations and during the second period 5,318 operations were performed. Two hundred thirteen deaths occurred during the first period but there were only 69 in the second. The mortality rate was 3.5 per cent for the first period and 1.3 per cent for the second period. There was a steady decrease in the number of deaths, the least number being recorded in 1946 and 1947 when the mortality rates were 0.70 and 0.67 per cent, respectively.

During the twelve years which elapsed between the two studies, the type of surgery performed underwent considerable change. There was a much greater tendency to remove part or all of the adnexa at the time of hysterectomy and if it was necessary to remove all the adnexa, then the uterus was also removed. In the recent period the number of total hysterectomies rose from 350 to 1.033. There was a large increase in the number of vaginal hysterectomies, 158 having been performed during the first period and 531 during the second period.

Peritonitis was the most frequent cause of death in both series. It was responsible for 48 per cent of the fatalities in the first period and 29 per cent in the second period. In 1946 and 1947 only 12.5 per cent of the deaths were due to infection and this further improvement was due to the use of penicillin. There were 35 deaths from hemorrhage and shock in the first period and only 13 in the second. The decrease was, in part, due to the development of the blood bank, permitting more widespread use of transfusions. The death rate from malignancy remained fairly constant, there being 16 deaths in the first period and 14 in the second. There was a marked decrease in deaths from pneumonia and atelectasis, there being 18 fatalities in the first period and only 4 in the second period. The decrease was due primarily to the sulfonamides, penicillin, early ambulation, and improved technique of anesthesia. There was a marked decline in deaths due to pulmonary embolism from 18 in the first period to 2 in the second.

The decrease in the number of postoperative deaths with the second study is the result of a combination of factors. Among them have been the use of the sulfonamides, penicillin, and streptomycin, better preoperative and postoperative care, improved surgery, the blood bank, and early ambulation. Of equal significance has been the reorganization of the Department of Gynecology of the Cook County Hospital and the development of a comprehensive plan of resident training.

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UNANTICIPATED FETAL RISKS IN THE PERINEAL STAGE OF LABOR

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THE obstetrician approaches the end of labor with confidence. The anxiety experienced during the dilatation of the cervix and the descent of the head is usually considered over. Capped and gowned he faces the delivery table feeling that he is now in complete command of the situation. Our records at the New York Lying-In Hospital, however, point out that occasionally there are hazards still facing the baby. From a study of the labor records of fetal deaths occurring at the end of the second stage it is possible to distinguish and classify the main causes of these fetal deaths. They are listed in the accompanying table.

Material

The cases in this study were selected to include only those in which fetal death occurred at full dilatation with the head on the perineum or well below the spines. All premature infants (less than 2,500 grams) and those babies with serious congenital anomalies were excluded, and, if there were reasons to suspect prior to the time that the vertex reached the perineum that a normal term spontaneous delivery (vertex presentation) could not be anticipated, the case was discarded. This, of course, excluded those patients with contracted pelves, toxemia, mid- or traumatic forceps, etc. With strict adherence to this set of standards, the group of deaths occurring with shoulder dystocia would not fit the criteria, for one should anticipate difficulty with the delivery of a large infant. However, since this complication falls within the time limit of the study, and since the estimation of fetal size may be very difficult and may not be anticipated, we have included these deaths. Thus, although we have a limited group of cases in which the obstetrician would expect a normal full-term infant either by spontaneous delivery or with prophylactic forceps, the infant succumbs. Undoubtedly, many additional infants were asphyxiated but survived because of resuscitation measures.

From a total of 1,135 full-term fetal deaths, of which 775 were stillborn or deadborn, only 38 cases were found to meet the above criteria. These 38 cases constituted 5 per cent of the stillborn or deadborn during the years 1932 through 1949 when 52,120 full-term infants were delivered. The infants in this series died from either complete asphyxia in utero or partial asphyxia which was severe enough to damage permanently and irreversibly the respiratory center. The autopsies showed the usual changes of anoxia, i.e., petechial hemorrhages in the tissues and/or atelectasis and aspiration of meconium. We know, however, that the infant has a considerable tolerance and an extraordinary reserve to combat asphyxia. We have seen women cyanotic with severe heart disease or with severe anemia, and yet they usually deliver live infants. Eastman[1] cites the case of a pregnant woman who delivered a normal child after having been so severely asphyxiated with carbon monoxide that artificial respiration was required for 20 minutes.

TABLE I. CAUSES OF FULL-TERM FETAL DEATHS IN THE PERINEAL STAGE FOLLOWING NORMAL LABOR IN UNCOMPLICATED PREGNANCIES

		DELIVERY		CONDITION	
	NO.	SPONTANEOUS	LOW FORCEPS	STILLBORN	DEADBORN
Cord complications	17	12	5	4	13
a. Cord around the neck or shoulder	14	10	4	4	10
b. Prolapse	1	0	1	0	1
c. Intrauterine rupture of cord	1	1	0	0	1
d. Compression of vessels (vasa previa)	1	1	0	0	1
Premature separation of the placenta	6	5	1	2	4
Excessive sedation	3	1	2	2	1
Shoulder dystocia	4	3	1	1	3
Prolonged second stage	3	1	2	2	1
Unknown	5	4	1	4	1
Total	38	26	12	15	23

Himwich and associates[2] have found that the infant rat can utilize an anaerobic source of energy to maintain life for 50 minutes, whereas the adult will survive for only 10 minutes. Nevertheless, although a margin of safety in the fetus does exist we are unable accurately to assess its limits. We are also aware of the fact that partial asphyxia in utero with the recovery of the infant after resuscitative measures is not always the answer. Windle[3] states that guinea pigs asphyxiated for periods of 8 minutes showed definite to marked central nervous system damage. Lund,[4] in a study of asphyxia in 2,006 consecutive deliveries, found 10 infants with permanent brain damage, 5 cases of which were attributed to asphyxia. We are, therefore, faced with the problem of recognizing asphyxia early enough in order to effect prompt delivery of a sound infant in a phase of labor when this may be accomplished readily.

Notwithstanding the fact that attention has been directed toward fetal salvage and fetal asphyxia in recent years, the only reliable index which we possess that is helpful in the recognition of anoxia is a sudden slowing of the fetal heart. It had been considered by some that tachycardia was of significance, but Bartholomew[5] showed that a fetal heart rate of 160 or above is not necessarily an indication of fetal asphyxia. Lund[6] also demonstrated this with an endocardiograph. Experimentally, occlusion of the umbilical cord was found to produce bradycardia[7] but it was not known whether the reaction was from vagal impulses or due to an altered chemical balance of the blood on the heart. In our series of cases, though some indication of fetal distress was discovered in only one-half of the infants, there was always a bradycardia and never a tachycardia.

The passage of fresh meconium is another sign which has been considered indicative of fetal asphyxia. Schulze[8] reported that the passage of meconium during labor occurred in 3 per cent of 5,534 deliveries and it was of negligible significance unless accompanied by changes in the fetal heartbeat, when it would signal profound asphyxia. Meconium did appear in combination with fetal heart rate changes in 9 of our cases, but its absence certainly did not preclude intrauterine distress. This is important, for some obstetricians feel that its absence is a favorable sign. Its presence sometimes precedes fetal heart rate changes.

Anoxia in utero will also induce premature respiratory efforts and thus promote an accumulation of amniotic fluid and meconium, if present, in the lungs. This, in turn, will act as a serious barrier to extrauterine respiration and oxygenation. Windle[3] has not been able to demonstrate the aspiration of amniotic contents experimentally unless asphyxial conditions were present.

He did not believe that a tidal flow of amniotic fluid exists with associated intrauterine respirations. However, Davis and Potter[9] have found that the fetus may exhibit respiratory movements in utero and that "in intrauterine fetal distress with its associated anoxia, the excitation of the respiratory mechanism results in exaggerated respiratory efforts, and the aspiration of large amounts of amniotic fluid, but death occurs not because of this excessive fluid, but because the fetal circulation has been embarrassed." They feel that "a prompt recovery from the resultant anoxia would probably lead to a rapid absorption of the fluid in the lungs." Irrespective of which may be the correct answer, it is a result of anoxia and one of the major problems to attack in asphyxiated infants after delivery. We have found, in 15 stillborn infants, that material had been aspirated during labor. These infants died, nevertheless, despite suction and the administration of positive pressure oxygen.

Cord Around the Neck

Of the 14 infants with the cord around the neck, 10 were deadborn and 4 were stillborn. The cord lengths varied from 20 to 76 cm., with an average of 53 cm. Ten infants were delivered spontaneously and 4 by outlet forceps. Fetal bradycardia, or change in the rate of the heart, occurred first in 1 case 1½ hours before delivery, and in 2 others, 55 and 45 minutes prior to the birth of the child. In 6 cases, alteration in the rate was recorded within 30 minutes or less of delivery. In the remaining 5 cases either no notation was in the record or no change was noted. Presumably, all of these deaths are preventable; but we realize that there are times when it may be virtually impossible to follow the fetal heartbeat as carefully as one would wish.

Three other infants died as a result of other cord complications. In two cases there was a velamentous insertion of the umbilical cord. In one, an intrauterine rupture of the umbilical cord occurred 30 minutes before delivery. The fetal heartbeat was lost abruptly and the site of rupture was 2 cm. from the placental insertion. In the other, as the patient was transported from the labor room to the delivery room, the membranes ruptured, and the infant was asphyxiated from compression of the vessels (vasa previa). Only 10 minutes elapsed between the rupture of the membranes and actual delivery, but in spite of this the infant was deadborn. The cords were 44 and 70 cm. long, respectively. The other case was a prolapse of the cord which escaped detection. After 1 hour in the second stage of labor this was discovered by a vaginal examination which was done because of an alteration in the fetal heart rate. This may have been a presentation of the funis at first which later descended further, so that it could be palpated finally.

Premature Separation of the Placenta

These cases numbered 6 and were fairly typical. The mothers all had perfectly normal labors, neither short nor violent. As the child was born a gush of blood accompanied the infant and the completely detached placenta followed shortly afterward. All were delivered spontaneously and 4 were deadborn, whereas 2 were stillborn. The immediate blood loss was estimated to vary between 100 to 400 c.c. and one patient required a transfusion for postpartum anemia. Of the deadborn, the fetal heartbeat was lost at 6, 15, 43, and 75 minutes before delivery. In the case of the 75 minute delay, the cord was 25 cm. long and the heartbeat was lost as the membranes ruptured and the head descended. This was the only short cord in the series and the descent of the fetus may very well have exerted enough traction on the placenta to separate it. However, the other cord lengths were between 42 and 58 cm., and averaged 49

cm. Stander[10] states that the traction of an abnormally short umbilical cord may produce a premature separation of the placenta in labor. Barclay, Franklin, and Pritchard[7] mentioned in their section on rupture of the umbilical cord that in a series studied by Shordania, all cords withstood 4.5 kg. of stress and that the average was 5.7 kg. Why the placenta should separate in some instances, while in others the cord ruptures, is impossible for us to state. In the case of the 25 cm. cord, the placenta had several small infarcts which were described as atypical. Three placentas were normal and 1 was found to have an endarteritis of the large vessels as well as the small ones supplying the villi. Another showed early fibrinoid degeneration.

In no case was there any acceleration of the fetal heart rate as described by Richardson[11] under conditions in which there is a small area of placental detachment. This fetal tachycardia is interpreted as a compensatory phase of asphyxia in cases of premature separation of the placenta, and the rate and degree of response should bear a definite relationship to the area of placental detachment. Perhaps the ones we have studied were so rapid and complete that the change was missed.

Shoulder Dystocia

Four cases are in this group and the weights of the infants varied between 4,600 and 6,280 grams. Three were delivered spontaneously and one by elective low forceps. In each case, of course, the heartbeat was lost during manipulation in attempts to deliver the shoulders. In one instance, the cord prolapsed during the extraction of the shoulders. Asphyxia may result not only from compression of the cord against the pelvic brim, but also from the enormous amount of blood which is transferred with each uterine contraction from the trunk to the head, giving rise to subsequent vascular congestion and possible hemorrhage.[1] The vascular system of the newborn is unable to withstand excessive vascular pressure. In retrospect, these patients should have been delivered by cesarean section.

Excessive Sedation

There were 3 cases in which excessive sedation may have been responsible for the death of the fetus. An enormous amount of literature has been written about the increased incidence of asphyxia with heavy sedation, yet sedation is still and probably will remain an important consideration in obstetrical practice. One patient received Nembutal 0.3 Gm., Demerol 100 mg., and scopolamine 0.6 mg., 3 hours before delivery, and then 1 hour later, Demerol 100 mg., Nembutal 0.1 Gm., and scopolamine 0.4 mg. Ten minutes before delivery the fetal heart rate was 140 and the fetal heartbeat was lost 5 minutes later. Delivery was accomplished with low forceps and a deadborn infant resulted. No cause was found, but one can only speculate in a case of this sort for the supply of oxygen is still dependent on the integrity of the maternal circulation. We doubt whether the maternal alveolar oxygen is reduced enough under this condition to affect the medullary centers of the fetus. Another patient received 15 c.c. of paraldehyde 7½ hours and 3 hours prior to delivery and the infant was stillborn. At autopsy the tissues of the infant's brain contained 0.25 per cent concentration of paraldehyde, and the examiner felt that this was equivalent to a 2+ alcohol level. Bodansky,[12] in the discussion of Kotz and Kaufman's paper on obstetric analgesia, felt that one can only speculate. "It is conceivable," he says, "that, though a transient rise in the concentration of paraldehyde in the blood and tissues of the fetus may be of little consequence, a high level of concentration sustained for many hours may produce quite a different effect, the pathological changes of which nothing is known at present."

Finally, one case was found in which, at autopsy, a hemothorax and atelectasis accompanied hemorrhages in the lungs. Here not only is the question of sedation present, but the fact remains, perhaps, that too vigorous resuscitation may have been carried out. Caution should be exercised in using too much positive pressure of oxygen; attempts at artificial respiration may likewise be responsible for lung trauma resulting in a hemothorax and hemorrhages in the lungs.

Prolonged Second Stage

Three cases were in this group and were placed in this category for the prolonged second stage was the only factor which was unusual. It was the impression of the authors that when the second stage was prolonged, other factors usually predominated which predisposed to this extension of labor. Many fetal deaths in this group were excluded because of midforceps, contracted pelves, desultory labors, etc. Perhaps prolonged second stages in normal labors without associated abnormality may not be as serious a problem as presumed, though Cole, Kimball, and Daniels[13] in their report on "Neonatal Asphyxia" conclude that the incidence of asphyxia increases with the duration of the second stage. All were stillborn and one was delivered spontaneously, the other 2 with outlet forceps.

Unknown

In 5 cases no reason for the fetal death could be discovered. Four were stillborn and one was deadborn. Four were delivered spontaneously and one by low forceps, and this was for fetal distress. The mothers did not receive too much sedation and the labors were not precipitate.

It is to help in reducing some of these fetal risks that a brief discussion of the mechanism and management of the perineal stage of labor is presented. While avoiding damage to the maternal tissues is often the chief concern of the doctor in the average delivery, the welfare of the baby must always be uppermost in the accoucheur's mind. Many refinements of the perineal technique may have to be abandoned instantly if fetal distress becomes evident. Intensive observation of the fetal heart rate is always of prime importance as the head approaches the perineum. It is customary to ignore a dropping of the rate to 80-90 just after a contraction if it promptly rises to 120-130. However, this may be a warning of dangerous cord tension due either to a short cord or one further shortened by tight coils around the neck.

By the time the vertex is on the perineum, the umbilicus is just passing the pelvic brim. The cord lying loosely on the abdominal surface of the baby is usually protected from pressure by the small parts also lying on the anterior abdominal surface. However, an occult prolapse of the cord below the pelvic brim can also be the unrecognized cause of the intermittent slowing of the fetal heart rate, and it is evident that such situations cannot be allowed to go on too long without resort to Kristeller fundal pressure, episiotomy, or low forceps for more prompt termination of the delivery. Under such circumstances, while preparing the patient for delivery, it is wise to place her in Trendelenburg position and to administer oxygen to the mother, as advocated by Waters and Harris,[14] and Lund.[15] Their observations on the supportive powers of oxygen in such a case, which may even result in the return of the fetal heart rate to normal, are convincing. Nevertheless, several babies have been lost when this combination of circumstances has lasted a half hour or longer. The old arbitrary rule whereby the head should not be permitted to remain more than one-half hour on the perineum without progress is a good one.

At this point it is highly important to avoid two errors in evaluating delay when the caput is visible; one when the cervix is well dilated but not yet re-

tracted and still grasps the head, and the other when growth of the edematous caput and molding of the head give a false picture of complete descent. Both situations can be determined only by a careful vaginal examination and either may shortly be as productive of fetal asphyxia as the more common causes of perineal delay.

It is well known that a difficult forceps operation on an already handicapped baby will only increase the fetal risk, but when the heart is persistently slowed after a pain and advance is also slow, the danger of a low forceps delivery carefully performed is undoubtedly less than that of waiting too long. Years before anesthesia was available skilful obstetricians[16] could apply forceps without the patient's knowledge. Gentle and accurate application of low perineal forceps may often be made with a minimum of anesthesia. Traction then made simultaneously with a uterine contraction should overcome the delay without further harm to the baby. A simple maneuver in developing good bearing-down efforts on the part of a sedated patient when the head is somewhat delayed at the bony outlet is to introduce the index finger of each hand about 3 inches to the lower edge of the levator muscle and press downward and outward simultaneously with a uterine contraction. This will usually result in an augmented effort on the part of the partially anesthetized mother which sets the head down on the backs of the fingers so that they must be quickly slipped out as the head advances.

The 3 classic obliquities of the head are retained even at the vulval orifice. One end of each cardinal diameter passes alone, never simultaneously with the opposite end. This is especially important with the occipitofrontal diameter and flexion should be maintained until one parietal boss and then the other is delivered. It is thus best to maintain flexion until the larger part of the head has escaped from the vulva. By this time, the occipital end of the occipitofrontal diameter is born, the bulge of the perineum has flattened out, and there is more room for encouragement of extension of the head. Both Gammeltofft and Kjelland, when visiting at the New York Lying-In Hospital many years ago, criticized our too early use of the Ritgen maneuver. They preferred keeping the head well flexed until the suboccipitobregmatic circumference was delivered. It is then time enough to institute the modified Ritgen maneuver for extension. Folds about the clitoris and labia minora may be tucked back with the lubricated finger but never the posterior edge of the thinning rim. With all conditions satisfactory, it is of advantage to complete the delivery of the head between pains in order to control too rapid advance.

Episiotomy is generally the procedure of choice in primigravidas. Ironing out the perineum can be overdone and often initiates the very damage it is supposed to avoid. While a young primigravida at times is delivered without episiotomy or laceration, preserving an intact perineal body is often at the expense of irregular lacerations of the upper portion of the labia minora extending toward the urinary meatus and clitoris. In addition, it is not wise to play the integrity of the perineum against the fetal heart rate. In asphyxia a deep and prompt episiotomy is always helpful. It might be noted here that most mediolateral episiotomies cut too far into the skin surface. For more room additional snips should be made in the vaginal tissues. When these tissues are rigid an incision further up the vagina may also be necessary to avoid a sulcus tear.

After delivery of the head the baby's face turns purple and it appears to be rapidly developing a state of asphyxia. A tendency to hurry this part of the delivery should be resisted. In the interval before the succeeding uterine contraction the baby's eyes may be wiped off, mucus removed from the mouth and nasal passages with a soft rubber syringe, search made to relieve cord coils about the neck and to diagnose the position of the shoulders. The

importance of this interval has been stressed by Dieckmann[17] and others in assuring better physiological separation of the placenta, restitution of the head and internal rotation of the shoulders. While the posterior shoulder is restrained with manual pressure against the perineum the anterior shoulder is delivered by gentle traction downward on the head assisted by firm pressure on the fundus by the assistant. The first sign of impending trouble with the shoulders is an unusually tight fit of the head against the perineum after its delivery. Too much effort at this point will result in brachial birth palsy and too much delay will sacrifice the infant's life. The best procedure with impacted shoulders in a large baby is prompt deep mediolateral episiotomy or definite extension of an episiotomy already made, and dislodgment of the posterior shoulder by passing the hand well up into the hollow of the sacrum sweeping the posterior arm down across the baby's chest. One baby was lost while the attendant attempted to bring the arm down across the back. Fracture of the clavicles by thumb pressure has been proposed when the shoulders are impacted, as well as actual cleidotomy, but the authors have never been forced to employ either of these measures.

If the baby is in good condition it is wise, if feasible, to delay tying the cord until pulsations have ceased. There are two reasons for this: first, the baby has been proved to receive as much as 90 c.c. of blood from the placental circulation and, second, the cord shrinks markedly after pulsation has stopped and a small mass to tie insures better ligation.

Summary

The obstetrician has every reason to expect a normal infant once the vertex has reached the perineum after a normal labor and an uncomplicated antepartum course. The authors have found, however, that hazards still face the infant at this time.

A study was undertaken to determine the number and nature of these unanticipated full-term fetal deaths which occurred in the terminal phase of labor. From 1932 through 1949, 52,120 full-term deliveries were conducted at the New York Lying-In Hospital. In this group were 1,135 full-term fetal deaths, of which 775 were stillborn or deadborn. Thirty-eight, or 5 per cent, satisfied the criteria of this study and could be called unanticipated fetal deaths.

Cord complications ranked highest; 14 infants were asphyxiated from anoxia secondary to cord coils around the neck or shoulder. In addition, 1 vasa previa, 1 intrauterine rupture of the umbilical cord, and 1 prolapse of the cord contributed to the fetal mortality. In this group short cord was of no particular significance.

Late premature separation of the placenta followed with 6 cases. No compensatory acceleration of the fetal heartbeat, as described by Richardson,[11] was detected. Although a short cord is believed to be a major contributing factor we were unable to substantiate this claim. Examination of the placenta did not reveal any consistent abnormality.

Shoulder dystocia was responsible for 4 deaths and occurred in infants between 4,600 and 6,280 grams. Though theoretically complicated by excessive weight, we have included this group since estimation of the fetal size is a difficult problem. Prolonged second stage and excessive sedation each added 3

cases to the group. Some question as to the interpretation of these cases would, undoubtedly, exist, but when consideration was given to each individual case the authors felt that they should be placed in one or the other category. Finally, no apparent cause for fetal death could be found in 5 cases.

Fetal death was always signaled by a bradycardia and never a tachycardia. The presence of fresh meconium coupled with fetal heart deceleration heralds profound and terminal asphyxia, but an absence of meconium does not preclude anoxia in the presence of a bradycardia. A brief discussion of the physiological aspects of anoxia relative to this problem is presented. Consideration of the management of the perineal stage of labor and subsequent delivery has also been considered.

Conclusions

1. It is evident that some further reduction in fetal mortality can be accomplished if signs of asphyxia at the end of the second stage are promptly heeded.

2. With the caput in sight the obstetrician must be constantly alert as to the possibilities and immediate handling of cord pressure, prolonged perineal delay, occasional late premature separation of the placenta, as well as impacted shoulders in large babies.

3. Careful and frequent auscultation of the fetal heart should be carried out during the perineal stage of labor and one should entertain the idea of delivery after one-half hour in the perineal stage.

4. Sterile vaginal examinations should be frequently employed.

5. Cesarean section at times may be more expedient than vaginal delivery of excessively large infants.

6. The judicious use of sedation, especially in rapidly progressing labors, is important.

7. Finally, an understanding of the physiology of anoxia, and the gentle and careful use of resuscitation are required.

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PROLAPSE OF THE UMBILICAL CORD

An Analysis of 116 Cases at the Cincinnati General Hospital

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PROLAPSE of the umbilical cord represents an extremely serious and usually unpreventable obstetrical accident. The average incidence is said to be approximately 1 in 200 deliveries and, because of this frequency, further study of the possible etiological factors, causes of fetal mortality, and optimum method of treatment is of importance.

For the purpose of classification, cord prolapse has been divided into 3 major groups: 1. *Occult type,* occurring when the cord is at or near the lower uterine segment but not within reach of the fingers during the ordinary examination. 2. *Forelying type,* palpable by the examining finger through the cervix, but with the membranes intact. 3. *External type,* with membranes ruptured, cord is actually extruded through the cervix into the vagina and occasionally outside the vulva. In this paper only the external type will be considered.

Material

This study represents an analysis of 116 consecutive cases of prolapsed cord occurring on the Obstetrical Service of the Cincinnati General Hospital during the period 1940 through 1949.

All deliveries were performed by members of the resident staff, interns, or medical students. This hospital possesses no private service, all cases being under the direct supervision of the Chief Resident. In many cases, because of the exigency of the situation, quick delivery was performed by an intern or junior resident, without benefit of staff consultation.

Incidence

During the period of analysis there were 24,533 deliveries, the 116 cases representing an incidence of 0.47 per cent. This figure is in agreement with those previously reported by Kurzrock,[1] Mengert,[2] Draa,[3] Hillis,[4] and Burgeois[5] (Table I).

TABLE I. INCIDENCE

DATE	AUTHOR	HOSPITAL	TOTAL DELIVERIES	NO. OF CASES	INCIDENCE %
1932	Kurzrock	Brooklyn Jewish	16,942	100	0.59
1940	Mengert	Iowa	9,546	58	0.66
1940	Longwell Draa	Chicago Presbyterian	5,035	18	0.35
1940	Hillis	Cook County, Chicago	9,581	25	0.26
1941	Bourgeois	Providence Living-In	36,773	155	0.42
1950	Brandeberry Kistner	Cincinnati General	24,533	116	0.47

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Etiology

Table II shows an analysis of this incidence according to presentation. It is known that the major etiological factor in prolapse of the cord is maladaptation of the presenting part to the lower uterine segment, resulting in the malpresentations, transverse and breech. Twelve per cent of the transverse presentations and 4.5 per cent of the breech presentations were complicated by prolapse of the cord. Only a small number accompanied the vertex presentation, 0.25 per cent. These figures parallel very closely those of Mengert.[2]

TABLE II. INCIDENCE OF PROLAPSE OF CORD ACCORDING TO PRESENTATION

AUTHOR	VERTEX %	BREECH %	TRANSVERSE %
Mengert	0.37	4.54	14.27
Brandeberry	0.25	4.58	12.0
Kistner			

The usual etiological associations of prolapse cord are: contracted pelvis with a floating head, extremely long cord, polyhydramnios, twins, lowly implanted placenta with velamentous insertion, prolapsed arm, and the malpresentations already noted. The cord may prolapse also during obstetric operations such as breech extraction, internal podalic version, and, especially in this clinic in the past, following expulsion of the hydrostatic bag. In a recent study[6] it was shown that the cord prolapsed in 9.8 per cent of 244 cases where the bag was utilized.

The various causes of cord prolapse in this study are listed in Table III. Thirty-one per cent of the total cases occurred in breech presentations, 22.4 per cent followed the expulsion of the hydrostatic bag, and 10.4 per cent occurred with transverse presentations. Twins accounted for 7.7 per cent of the total, and with infants weighing over 4,000 grams the cord prolapsed in 3.4 per cent of the cases. In 20 per cent of the cases, no known etiological factor was found.

TABLE III. ETIOLOGY

MAJOR FACTOR:	NUMBER OF CASES	% OF TOTAL
Breech	36	31
Bag	26	22.4
Transverse presentations	12	10.4
Twins	9	7.7
Infant over 4,000 grams	6	5.2
Infant under 1,500 grams	4	3.4
Contracted pelvis	3	2.6
Failed forceps	3	2.6
Face presentations	1	0.9
Polyhydramnios	1	0.9
Excessively long cord	1	0.9
Unknown	24	20.7

Race and Age

Table IV shows the incidence of prolapsed cord and associated fetal loss according to race. The incidence is slightly higher and the fetal loss somewhat greater in the Negro patient. In the 10 year period of this study, 54 per cent of the total deliveries were in Negro patients, and 46 per cent in white patients.

Maternal age was of no significance either in incidence or fetal loss. The oldest patient in this survey was 44 years old, the youngest 14, and the average age was 27 years.

TABLE IV. RACE

RACE	NUMBER OF PATIENTS	%INCIDENCE OF PROLAPE	FETAL MORTALITY RATE
White	50	0.44	22.0
Negro	66	0.52	37.9

Parity

Table V shows the incidence, total number of cases, and the gross fetal mortality rate in the primigravida and the multipara. It is evident that prolapsed cord occurred almost four times as often in the multipara but the clinic incidence was only slightly higher in this group. The fetal mortality was appreciably higher in the multiparous patient. There were 12 patients who could be classified as "grand" multiparas (para viii or over).

TABLE V. PARITY

	INCIDENCE	NUMBER OF CASES	GROSS FETAL MORTALITY RATE %
Primigravidas	0.34	25	20.0
Multiparas	0.52	91	34.0

Rupture of the Membranes

Table VI outlines the method of membrane rupture. Thirty-seven per cent of the cases had artificial vaginal amniotomy and in 63 per cent of the cases the membranes ruptured spontaneously. The incidence of prolapsed cord in the entire clinic following vaginal amniotomy is 1.0 per cent.

TABLE VI. RUPTURE OF MEMBRANES

	NUMBER	%	FETAL MORTALITY RATE %
Artificial	43	37.0	20.9
Spontaneous	73	63.0	42.4

The fetal mortality was twice as high in cases where the membranes ruptured spontaneously, obviously due to delay in recognition of the prolapsed cord and incomplete cervical dilatation at the time of rupture.

Vaginal amniotomy is performed only rarely for the induction of labor in this clinic. When it is done the following criteria must be met: (1) The vertex must present and must be engaged. (2) No portion of the cord may be palpable. (3) The cervix must be "ripe," that is, soft, not over 1 cm. in thickness, and the examiner must be able to introduce 1, and preferably 2 fingers through the internal as well as the external os.

The time interval from membrane rupture to delivery had no effect on fetal loss but the length of time elapsing between recognition of the prolapsed cord and delivery appears significant. The average elapsed time from recognition to delivery was 9 hours and 2 minutes in the stillborn group, but was only 57 minutes in the cases where liveborn infants were delivered. The average elapsed time for all cases was 3 hours and 30 minutes.

Maternal Morbidity and Complications

Twelve patients were classified as morbid by the standard criteria of temperature elevation of 100.4° F. or above on any two puerperal days excluding the first twenty-four hours. The incidence of morbidity is, therefore, 10.3 per cent, somewhat higher than the clinic average of 7.8 per cent reported by Pierce[7] for the years 1936-1946.

At the present time all cases of prolapsed cord in which intrauterine manipulations are necessary are treated with prophylactic penicillin.

No other complications were encountered.

Fetal Mortality

The fetal mortality is shown in Table VII. There were 41 fetal deaths in this study, a gross fetal mortality rate of 35.3 per cent. Thirty-six of these babies were deadborn and 5 died neonatally. This fetal loss is appreciably less

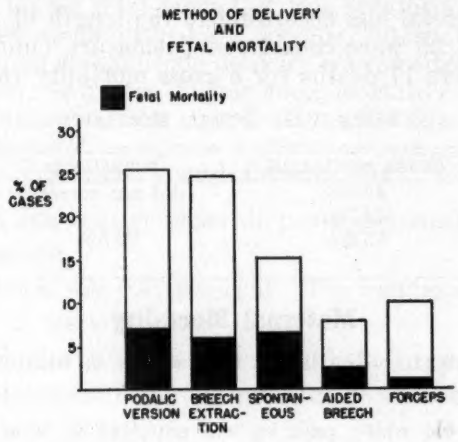

Fig. 1.—Gross fetal mortality according to method of delivery.

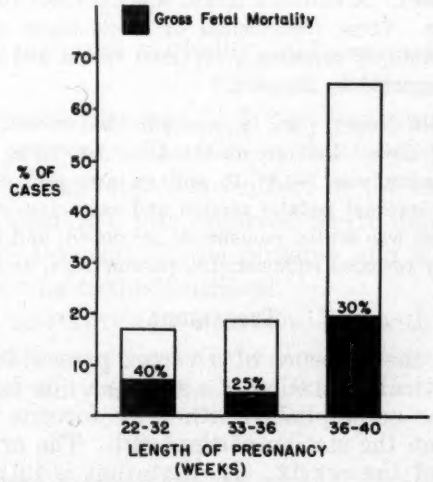

Fig. 2.—Gross fetal mortality in relation to length of pregnancy.

than that reported by previous authors.[2,5] The corrected* fetal mortality rate was 29.3 per cent and if further corrected† for "treatable" cases, the fetal mortality rate is reduced to 21.5 per cent.

Fig. 1 graphically reveals the gross fetal mortality rate according to the method of delivery. The highest rate occurred in the cases where spontaneous delivery was awaited (42 per cent). Lower rates occurred with internal podalic

*Correction factor: Infants weighing under 1,500 grams and/or having congenital abnormalities incompatible with life.

†Correction factor: Cases in which there was no fetal heartbeat on admission.

version (26 per cent) and with breech extraction (25 per cent). In aided breeches the fetal loss was 33 per cent and with forceps delivery 12.8 per cent.

There were 21 cases in which prolapse of the cord was discovered when there was less than 5 cm. dilatation and a fetal heartbeat present. In 14 of these a hydrostatic bag was utilized to secure dilatation and in this group the fetal mortality rate was 57 per cent. Seven cases were allowed to proceed without any treatment except knee-chest position and displacement of the presenting part. In this group the fetal mortality rate was 71 per cent. There was one infant who weighed under 1,500 grams in this group so the corrected fetal mortality rate for the cases with cervical dilatation less than 5 cm. is 57 per cent.

Fig. 2 shows the fetal loss according to the length of gestation.

Of the 116 cases, 35 were considered premature (under 2,500 grams) and in this group there were 17 deaths for a gross mortality rate of 48.6 per cent.

TABLE VII. FETAL MORTALITY

AUTHOR	GROSS MORTALITY	CORRECTED	TREATABLE
Mengert	46.0%	(did not correct)	
Bourgeois	49.7%		40.6%
Brandeberry Kistner	35.3%	29.3%	21.5%

Maternal Mortality

There were 2 maternal deaths in this series, a maternal mortality rate of 1.7 per cent.

CASE 1.—A 34-year-old white, para iv, was admitted at term with a history of membranes having been ruptured for 1 week, chills and fever for 2 days. The temperature was 100.4° F. Five days after admission labor ensued spontaneously and shortly thereafter a prolapsed cord was diagnosed. A stillborn infant was delivered followed by excessive hemorrhage and uterine packing. Three transfusions of whole blood were given but the patient died the following day. Autopsy revealed a ruptured spleen and bilateral pneumonia. This case has previously been reported by Shannon.[8]

CASE 2.—A 39-year-old Negro, para ix, was admitted in active labor with a history of ruptured membranes for 3 days. Delivery in the home had been attempted by a physician. The temperature on admission was 102.3° F. and an arm and cord were found prolapsed. Under ether anesthesia an internal podalic version and extraction of a macerated infant were performed. The puerperium was septic, pneumonia developed, and the patient expired 12 days after adminssion. Autopsy revealed endometritis, parametritis, and bilateral pneumonia.

Treatment

Prolapsed cord in the presence of a vertex presentation with a living baby and with adequate cervical dilatation is a sine qua non indication for immediate delivery. This may be accomplished either by forceps or by internal podalic version, depending upon the station of the head. The crux of the situation lies in correct evaluation of the cervix. If dilatation is incomplete, immediate delivery is dangerous for the child if a version is elected and dangerous for the mother if operative forceps are done—unless Dührssen's incision may be easily accomplished.

Prolapse occurring with a partially dilated, thick cervix necessitates immediate action and nicety of obstetrical judgment. The patient is placed immediately in the knee-chest position and the presenting part is displaced from the pelvis. Mengert[2] favored continuation of labor in this position and felt that cord replacement and the introduction of a hydrostatic bag are almost universally unsuccessful. He stated further that cesarean section is rarely indicated.

McCormick[9] suggested replacement of the cord with a repositor but stated that temporization with this method greatly decreases the chances of a live baby.

Cesarean section was suggested if the patient is an elderly primigravida or if the pelvis is moderately or severely contracted. Stander[10] favored cesarean section when prolapse has occurred with minimal cervical dilatation. Where cesarean section is contraindicated, replacement with a repositor was suggested.

When breech or transverse presentation exists, treatment is much the same, delivery by extraction or version at complete dilatation or cesarean section when the cervix precludes early delivery.

When the infant is assuredly dead, no definitive treatment should be attempted.

In this study the lowest fetal mortality was obtained in those cases where immediate delivery was accomplished by forceps, internal podalic version, or breech extraction. Where spontaneous delivery was awaited, the fetal mortality rate was almost doubled. An even higher fetal mortality rate existed in cases in which cervical dilatation was less than 5 cm. at the time of diagnosis.

Summary and Conclusions

1. A study of 116 consecutive cases of prolapsed cord occurring during a 10 year period is presented.

2. The clinic incidence was 0.47 per cent. The incidence was slightly higher in the Negro race and in the multipara.

3. The major etiological factors were breech and transverse presentations and the use of the hydrostatic bag. In one-fifth of the cases no cause was demonstrable.

4. Thirty-seven per cent of the cases followed artificial rupture of the membranes. The incidence of prolapsed cord following vaginal amniotomy was 1.0 per cent.

5. The incidence of maternal morbidity, 10.3 per cent, is somewhat higher than the clinic average.

6. The gross fetal mortality was 35.3 per cent and the corrected fetal mortality rate was 29.3 per cent. The fetal mortality was higher in the Negro, in the multipara, and where spontaneous rupture of the membranes occurred.

7. The lowest fetal mortality rate occurred where delivery was carried out in less than 1 hour after discovery of the prolapse and where forceps, version, or breech extraction were the methods utilized.

8. The highest fetal mortality rate was associated with spontaneous delivery and cervical dilatation of 5 cm. or less at the time of diagnosis.

9. The maternal mortality rate was 1.7 per cent.

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THE IODOACETATE (HUGGINS) INDEX IN PREGNANCY*

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Huggins, Miller, and Jensen,[1] and Huggins[2, 3] have shown that the coagulability of the blood serum is decreased in most persons with cancer, and, further, that this is not a phenomenon specific to the serum of cancer patients alone. Among the conditions, other than cancer, that frequently show lowered coagulability is pregnancy.[3] In this paper we are reporting our experience with the sera of 173 pregnant patients some of whom were able to re-examine at the time of parturition and again six weeks post partum.

Material

Methods used were essentially those of Huggins, Miller, and Jensen[4]:

Reagents: (1) M/15 phosphate buffer of pH 7.4. This was made up in water according to Huggins' first method[1] rather than in sodium chloride solution.[4] (2) M/2 sodium iodoacetate, recrystallized.[1, 4] 2.325 Gm. dissolved in a small amount of phosphate buffer (Reagent 1) and neutralized to phenolsulfonphthalein with 5.0 M sodium hydroxide, and then made up to 25 c.c. with the phosphate buffer.

Procedure: To a series of seven 10 c.c. volumetric flasks are added the amounts of 0.5 M iodoacetate solution (Reagent 2) shown below.

FLASK NO.	IODOACETATE SOLUTION C.C.
1	0.36
2	0.48
3	0.54
4	0.60
5	0.66
6	0.72
7	0.78

The content of each tube was then diluted to 10 c.c. with the M/15 phosphate buffer. All solutions containing iodoacetate were prepared fresh daily.

For each serum a series of seven 13 × 100 mm. Pyrex tubes was set up. To each tube was added 0.5 c.c. of serum followed by 1.0 c.c. of iodoacetate Solution 1 to Tube 1, 1.0 c.c. of iodoacetate Solution 2 to Tube 2, etc. Thus the tubes contained the following amounts of iodoacetate:

Tube No.	1	2	3	4	5	6	7
μ M iodoacetate	18	24	27	30	33	36	39

The contents of the tubes were mixed and the tubes placed in a vigorously boiling water bath for 30 minutes. At the end of the boiling the tubes were

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placed in ice water and allowed to stand again for 30 minutes. The coagulum was loosened from the tube with a close fitting loop of No. 8 piano wire and coagulation was determined by sliding the contents gently onto a No. 8 mesh wire screen with wire diameter of 0.7 mm. as described by Huggins, Cleveland, and Jensen.[3] "If the heated serum remains on the screen for one minute without an appreciable quantity dropping therefrom, the serum is defined as clotted; otherwise, it is liquid." The tube containing the greatest amount of iodoacetate in which the contents are solid is taken as the endpoint. The index is calculated from the iodoacetate content (in the endpoint tube) and the concentration of protein in the serum used. The Huggins procedure[1, 4] calls for 30 minutes' incubation at 98 to 100° C., the boiling point of water in Chicago. After trying several saline and nonaqueous baths in order to raise the incubation temperatures and varying the time of incubation, we concluded that no material difference in the index would result if we used tap water in the bath and boiled for 30 minutes at 93 to 95° C., the boiling point of water in Denver. Pollak and Leonard[5] ". . . found that the incubation period of thirty minutes could be safely shortened and final readings could be made after twenty minutes from the moment the test tube rack was placed in boiling water."

Plasma proteins were determined in approximately the first half of this series by the Kjeldahl micro-method of Hill and Trevorrow.[6] However Kjeldahl micro-methods for serum protein determinations are unnecessarily refined when the uncertainties of the other manipulations of the test are considered. For this reason, in the latter half of the series, the copper sulfate specific gravity method of Phillips and co-workers[7] was used with the saving of considerable time.

The Iodoacetate Index as calculated by Huggins and associates[4] gives great weight to the serum protein concentration. In the formula, I. A. I. $= \frac{\mu \text{ M acetoacetate} \times 2}{P}$, P is the serum protein concentration in grams per 100 c.c. If the plasma protein is very low an unduly high index is found. Thus pathological cases with low protein values may be thrown into the normal range. Conversely, if the plasma protein is unusually high a normal plasma may be thrown into the pathological range. For this reason we have compared the index, as calculated by the Huggins formula, with an index in which the square root of the protein concentration is used. Thus the serum protein concentration is a factor in the calculation, but is given less weight. The formula is: N. I. A. (New Iodoacetate Index) $= \frac{\mu \text{ M iodoacetate} \times 0.75}{\sqrt{P}}$. The numerator constant 0.75 is used instead of 2.0 in order to bring the dividing line between normal and pathological indices at the same numerical value as in the Huggins formula, thus making the two directly comparable. The square roots of serum protein concentrations can be read from tables found in any of the commonly used handbooks.

Experimental: In this series, sera from 173 pregnant patients were compared with the sera of 148 healthy controls. The controls were medical students, doctors, nurses, and other employees of the hospital. No patients were used as controls, for it was found that greater variations occurred among patients presenting themselves at the clinic even for very minor illness than among the former group.

Results and Comment

Fig. 1 shows a histogram of the iodoacetate indices of the 148 control sera calculated by the Huggins formula. Of the 148 cases, 17 (11.5 per cent) show values below 9, that is, 17 are in the pathological range according to

Huggins and his associates,[1, 4] who report no values below 9 in the sera from healthy persons. Kiefer, Sullivan, and Littlefield[8] reported none below 9.3 in a series of "700 apparently healthy men and women of various ages at a large Army Training Center." But Clifton[9] found 10 indices below 9.0 (22.8 per cent) in a series of 42 subjects with "no apparent disease."

Our control subjects range in age from 18 to 77 years, however, no correlation between age and the numerical value of the index could be found. Perhaps it should be expected that in any group of "normals" such as ours, a group in which none complained of illness, a few should respond positively to a nonspecific test. In a group of 51 patients who appeared on the wards and outpatient services of the Colorado General Hospital for minor illness, we found that 22 (43.1 per cent) showed indoacetate indices below 9.0.

The distribution of the iodoacetate indices (Huggins) of the sera of 173 normal prenatal patients is shown in Fig. 2. Of the 173 patients, 134 (77.5 per cent) show indices below 9.0 and 39 (22.5 per cent) show indices of 9.0 or above.

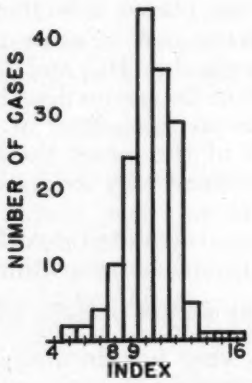

Fig. 1.—Controls, 148 cases. Nomagram showing distribution of iodoacetate indices calculated according to Huggins formula: $I.A.I = \frac{\mu M \times 2}{P}$; 11.5 per cent below 9.0; 88.5 per cent 9.0 or above.

When the nomogram of Fig. 1 (controls calculated by the Huggins formula) is compared with the nomograms of Fig. 3 (the same sera calculated by the formula using the square root of the serum protein concentrations) little difference is seen in the distribution above and below 9.0; 12.8 per cent are below 9.0. However, when the nomogram of Fig. 2 (prenatal cases, Huggins formula) is compared with that of Fig. 4 (prenatal cases, $\sqrt{P}$ formula) an interesting difference is seen. The distribution of the iodoacetate indices by the Huggins formula is 134 (77.5 per cent) below 9.0 and 39 (22.5 per cent) 9.0 or above. When the $\sqrt{P}$ formula is used with the same data 148 indices (85.5 per cent) are found below 9.0 and 25 (14.5 per cent) 9.0 or above. Thus 14 have crossed over the critical boundary. Furthermore, among those indices already below 9.0 there is a noticeable shift toward still lower values (Figs. 2 and 4). Our contention that the Huggins formula gives too much emphasis to the serum protein concentration is borne out by these results. Of the 173 in the series of prenatal cases 15 had total serum protein values below 5.0 Gm. per 100 c.c. Calculated by the Huggins formula 10 of these had iodoacetate indices above 9.0. When calculated by the $\sqrt{P}$ formula only 2 of the same 15 sera had indices above 9.0. Thus of the 14 cases that were changed from indices of "9.0 or above" to "below 9.0" by using the

$\sqrt{P}$ formula, 8 had total serum protein values below 5.0 Gm. per 100 c.c. Of the other 6 only one had a protein value above 6.0 Gm. Among the control sera, the 2 formulas gave approximately the same distribution because in this group there were no low serum proteins.

Six weeks post partum we again determined the iodoacetate index for 39 of these patients. The index had increased in 13 cases and decreased in 17 and was unchanged in 9. The average prenatal index for the 39 patients was 8.0. Six weeks post partum the average index for the same 39 patients was 6.9. We have only 6 cases in which the index was run immediately post partum. Of these the mean prenatal index was 8.7, the mean value at parturition 5.9, and the mean value 6 weeks post partum 6.9. These figures imply that, at parturition, there is, usually, a decrease in the already low index and that it is slow in returning to normal. We are now collecting data that we hope will show the progressive changes in serum coagulability during and following pregnancy.

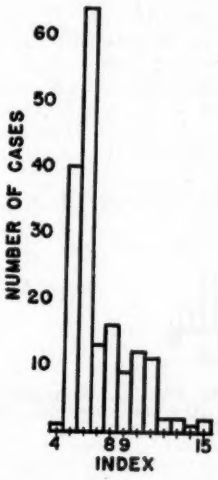

Fig. 2.

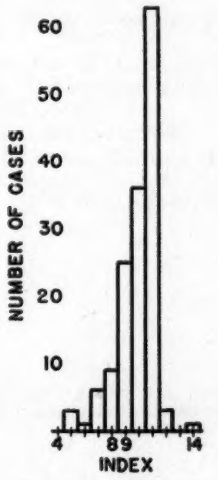

Fig. 3.

Fig. 2.—Prenatal, 173 cases. Nomogram showing distribution of iodoacetate indices calculated according to Huggins formula; 77.5 per cent below 9.0; 22.5 per cent 9.0 or above.

Fig. 3.—Controls, 148 cases. Same data as in Fig. 1. Nomogram showing distribution of iodoacetate indices calculated according to the square root formula: N.I.A. $= \frac{\mu M \times 0.75}{\sqrt{P}}$; 12.8 per cent below 9.0; 87.2 per cent 9.0 or above.

It is of interest to find that serum protein coagulability is decreased during pregnancy. Rapid neoplasia progressing within the uterus, a physiologic process, offers itself as a ready comparison to the cancer process. Neither growth is well understood but it is conceivable that a better understanding of normal placental and embryonic growth may lead to better understanding of abnormal growth.

Our earliest tests were taken at 6 weeks of gestation, others were taken throughout pregnancy and the puerperium. The stage of gestation had no correlation with the iodoacetate index. At first we thought that the hydremia of pregnancy and its normal lowering of plasma protein values might account for the decrease in coagulability. This we believe now not to be a factor since the formula for arriving at the index number has been adjusted to counter this possibility. Indeed, as we have shown, low serum protein values produce unduly high values of the Huggins index.

The Huggins Test is not diagnostic for cancer. The number of false positives and false negatives is too great. As a test for pregnancy the method has the same deficiencies. However, such tests may provide not only a tool for studying the various abnormalities of pregnancy, but also, in the individual patient, a measure of the degree to which the metabolism has returned to the pregravid state.

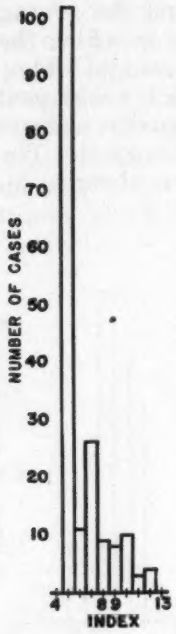

Fig. 4.—Prenatal, 173 cases. Same data as in Fig. 2. Nomogram showing distribution of iodoacetate indices calculated according to the square root formula; 85.5 per cent below 9.0; 14.5 per cent 9.0 or above.

It would be exceedingly interesting to know what system or element was responsible for a decrease in serum protein coagulability. Huggins[3] has suggested that the modification in the coagulability of serum is not caused by any changes in the protein itself but rather by the adsorption on the protein of anionic products of abnormal metabolism. Although the anionic products might be specific this method of testing is not specific. The different anionic products might be expected to have similar effects on protein coagulability.

Summary

The coagulability of serum protein (Huggin's iodoacetate method) was determined in 173 normal pregnancies and the Huggins Indices calculated. These values are compared with Huggins Indices determined on 148 healthy nonpregnant, individuals. In turn, using the same data, both of these are compared with indices calculated using a formula in which instead of the serum protein concentration the square root of the serum protein concentration is used. The square root formula minimizes the distorting effect of hypoproteinemia. By the Huggins formula, 11.5 per cent of the sera from healthy nonpregnant individuals show indices below 9.0, the low limit of normality according to the criteria of Huggins. By the square root formula, 12.8 per

cent fall below 9.0. In the 173 normal pregnancy cases the Huggins formula places 77.5 per cent of the indices below 9.0. Using the square root formula 85.5 per cent fall below 9.0.

Conclusions

1. The Huggins iodoacetate test shows too many false positives (11.5 per cent) and false negatives (22.5 per cent) to be used as a diagnostic test for pregnancy. When the square root formula is used the accuracy is improved (false positives 12.8 per cent) (false negatives 14.5 per cent) but still falls short of the desired specificity for a diagnostic test.

2. The test, using either formula, may have value in measuring the rate at which the metabolism of the parturient patient returns to the pregravid state.

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THE PLACENTAL METABOLISM OF VITAMIN A

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THE importance of the nutritional status of the fetus at the time of delivery is well recognized, and recent work has tended to indicate that fetal deficiencies—particularly of vitamin A—may be responsible for congenital abnormalities.[1, 2] Since the nutrition of the fetus depends not only on the maternal dietary intake, but, to an even greater extent, on the adequacy of transmission across the placental barrier, it becomes of increasing importance that the mechanism of such transmission be understood.

The present paper reports an investigation of the placental metabolism of vitamin A. In general, previous studies of vitamin A in the nutrition of the human fetus have been confined to determinations of the maternal and fetal plasma levels of carotene and of the vitamin.[3] Williamson has called attention to the placenta, however, by suggesting that in the rat the transfer of vitamin A across that organ is inversely proportionate to the placental fat content.[4] Furthermore, in the course of the previous work on the fetal metabolism of vitamin C,[5, 6] a knowledge of the placental levels proved invaluable. Accordingly, the status of the fetal nutrition with vitamin A has been reviewed from the point of view of its placental metabolism.

First Study

Since the majority of the studies herein reported are concerned with determinations made at the time of delivery, it became of importance to know the status of the mother at this period in her pregnancy. This question is a disputed one, Lewis[7] having reported a fall in maternal plasma A level during the last trimester, whereas Cayer[8] denies that such a drop in A level occurs. The former workers show that a maternal dietary supplement of vitamin A would prevent a drop in the maternal level (although it was without effect on the fetal level of A), whereas the latter workers found no need for A supplements.

Accordingly, it was felt desirable to know the relative status at the time of delivery of the women who were the subjects of this investigation. It must be stressed that this portion of the study was not designed to settle the differences of findings outlined above, but simply to ascertain any changes in plasma vitamin A in our particular patients at the conclusion of pregnancy. A dietician is attached to the Prenatal Clinic, and all of the women here studied had been given careful routine dietary instruction and supervision, and all of them received an iron-vitamin-calcium supplement which provided between 4,000 and 6,000 U.S.P. units of vitamin A per day.

A group of 20 women on such a program were studied during the last six weeks of pregnancy and the first six puerperal days. Plasma levels of carotene and vitamin A were determined at weekly intervals prenatally, and on alternate days in the puerperium. The results of this preliminary study are indicated

in Fig. 1. From this it can be determined that there is, in our patients, no great drop in plasma A levels in the closing weeks of pregnancy. There was, in the average for the group, a slight downward tendency in the postpartum carotene level, but the greatest change in plasma vitamin A shown by any individual patient was 1.0 gamma (from 0.7 to 1.7) per 100 c.c. plasma. It was felt from these findings that under the circumstances of the study the levels determined at the time of delivery were representative of the patient's general status and were not peculiarly altered by labor and delivery.

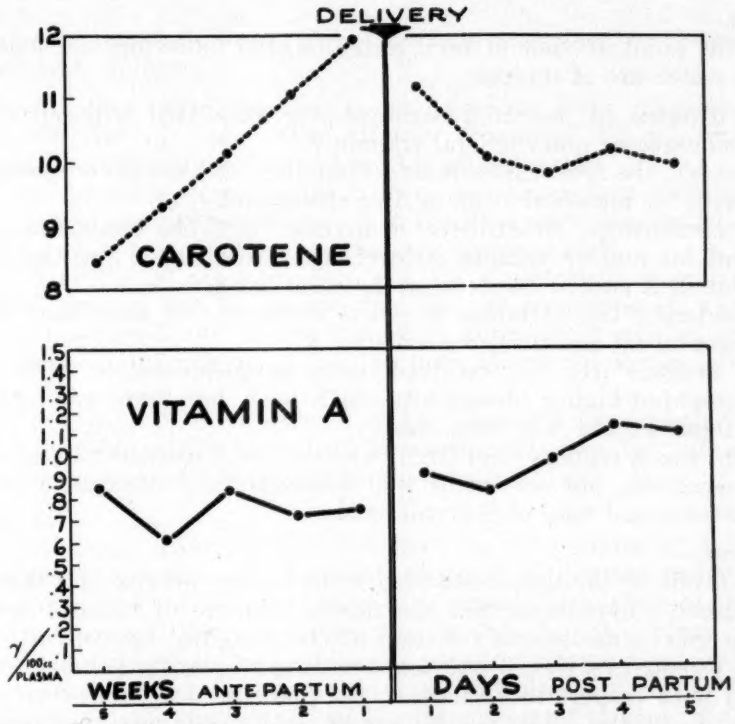

Fig. 1.—Average carotene and vitamin A levels prior to and after delivery of 20 patients on regular prenatal diet with vitamin supplement.

Second Study

Procedure and Assays.—

At the time of delivery maternal and fetal (cord) blood was collected, and the placenta obtained for analysis. The carotene, vitamin A, and cholesterol levels of the blood specimens were determined; the placentas were analyzed for total fat, carotene and vitamin A. The blood cholesterol was determined by the method of Sackett. Carotene and vitamin A were extracted and determined by Kimble's technique. Placental fat was determined gravimetrically using 5 to 8 gram specimens of ground tissue, and was recorded as grams of fat per 100 Gm. of placental tissue. It was extracted both by Bloor's method, and by the method cited by Williamson. The two extraction techniques yield amounts which are roughly but not mathematically proportionate; neither set of figures, however, alters the statistical conclusions reached as follows.

Sixty patients were studied. Fifty of them had been on the regular prenatal program without further supplementation; 10 had received an additional 100,000 units of vitamin A daily for 2 to 4 weeks prior to delivery. It is neither feasible nor necessary to record in detail the more than 500 determinations thus

made. The vitamin A levels ranged from 0.25 gamma to 1.9 gamma, and the carotene from 5.0 to 20.0 gamma per 100 c.c. The fetal plasma levels of both constituents were always lower than the maternal, ranging from 0.1 to 0.6 gamma for vitamin A, and from 0.0 to 6.5 gamma for the carotene. Placental fat showed a wide range in grams per 100 Gm. wet weight (2.0 to 14.8) depending on the method of extraction used. Maternal cholesterol levels were all within normal range, but the fetal levels were universally low, ranging from 77 to 142. The total data obtained in this study were submitted to analysis by the statistics laboratory of the Department of Mathematics.

Results.—

From the point of view of fetal nutrition, the following relationships were determined which are of interest:

1. An increase in maternal carotene was associated with an increase in both the fetal carotene and the fetal vitamin A.
2. However, the fetal carotene and vitamin A did not show specific changes associated with the maternal vitamin A or cholesterol.
3. No relationship—either direct or inverse—could be demonstrated between the placental fat and/or vitamin A level on the one hand, and the fetal blood levels of vitamin A and/or carotene on the other hand.
4. Considering the variables in pairs, there was no significant correlation between placental fat and placental vitamin A.
5. The mothers who had received heavy supplementation with vitamin A showed a somewhat higher plasma vitamin A level, but there was no significant increase in fetal vitamin A in these cases.
6. There was a tendency for high values of fetal cholesterol and of vitamin A to be associated, but we could not demonstrate a consistent relationship between maternal and fetal cholesterol levels.

Comment.—

The analysis of the data assembled from human pregnancies does not support Williamson's hypothesis that the rate of transfer of vitamin A across the placental barrier is an inverse function of the placental fat content. Furthermore, from conclusions Nos. 3 and 4 above, it can be argued that in contrast to its function with respect to vitamin C, the placenta does not serve as a depot for vitamin A storage. The results would tend to suggest (particularly Nos. 1 and 2) that the principal transfer to the fetus is in the form of carotene, and that once this transfer has been effected the regulation of the fetal vitamin A plasma level is a function of fetal metabolism, and is independent of the placenta.

Third Study

With these results available, further investigations were undertaken to complement these findings, and to delineate still further the metabolism of vitamin A. These investigations were directed toward a study of the fetal liver, and comparative assays of the carotene and A plasma levels in cord arterial and venous blood.

Procedure.—

The specimens of liver were obtained from non-macerated stillborn infants and (in three instances) from infants who died in the neonatal period. In the cases of the stillborn infants, the placenta was analyzed at the same time. In all of these tissue specimens carotene, vitamin A, and total fat were determined, using the assay methods indicated above.

Obtaining separate samples of cord arterial and venous bloods presented difficulties largely centering around the rapid thrombosis in the arterial system, and the increased need for anticoagulants in the arterial blood. The technique

ultimately adopted consisted of clamping the cord in the traditional manner on the placental side, but selectively clamping only the vein of the fetal side, cutting the cord between these clamps and permitting the arteries to bleed directly into the specimen bottle. The venous blood could still be drained from the cord after the arteries had thrombosed.

Twenty liver specimens were analyzed, and blood specimens were obtained from twenty infants. In two cases there was an overlapping, and the liver became available in babies from whom arterial and venous bloods had been obtained.

Results.—

The observations of interest from the data assembled in these studies can be summarized as follows:

1. The placenta contains more fat than does the liver, considered in grams of fat per 100 Gm. of tissue. The vitamin A storage did not prove in these cases to be a direct function of the fat level in either organ.
2. In the placenta, the vitamin A level was lower than the carotene level, both expressed in gamma per 100 Gm. In the liver, on the contrary, the vitamin A level was always very much higher than the carotene level.
3. In 14 of the 20 cases the carotene was significantly higher in the fetal venous blood than it was in the arterial. In the remaining six cases, the difference was not significant, or the two levels approached each other. In all of the cases, however, the vitamin A level in both bloods was the same (within 0.05 gamma per 100 c.c.).
4. While the level of vitamin A in the placenta was invariably less than that found in either of the two blood specimens, the liver tissue level of A was always many times greater than that found in either blood.

Comment.—

It would appear from these studies that the chief source of A for the baby is in the form of carotene which crosses in direct proportion to its level in the mother and is carried to the baby where it is converted to the vitamin. Nothing in our figures proves that this conversion necessarily takes place in the liver, but it does not take place in the placenta or the findings cited in No. 3 above would be reversed. The figures would tend to indicate that the fetal storage of A is in the liver (although not necessarily in proportion to its fat content), and that it is liberated to the baby's circulation very slowly (accounting for the similar arterial and venous levels).

Comment

In accounting for the constituents of the human fetus, two mechanisms have been, in the past, evoked: transplacental absorption from the maternal circulation and synthesis in the fetal tissues.[9] It would appear that both of these methods come into play in providing the fetus with a store of vitamin A. There was nothing in the present experiments which would indicate the time relationship involved in the transplacental transfers. The fact that, on a statistical basis, the mother who had a high plasma carotene level had a placenta richer in carotene and that her fetus had an increased plasma carotene does not indicate how long a period of time is required for this response to take place in any individual case. From the findings in a few patients given carotene, it would be our impression that a time lag of several weeks at least was involved. Certainly it is not analogous to the immediate fetal response to the administration of Vitamin C to the mother.[5]

It is obvious that if carotene crosses the placenta as a variable responding directly to the maternal level of carotene, then the fetal supply of vitamin A

as such is dependent primarily on the fetal ability to convert carotene. There is little reason to believe, furthermore, that this conversion rate in the fetus is governed in a significantly different manner than it is in the adult.[10, 11]

The factors leading to an adequate fetal supply of vitamin A, therefore, would seem to be a high maternal carotene level over a period of time together with a well-functioning ability on the part of the fetus to convert carotene to A. Once formed, the vitamin has a high affinity for the fetal circulation and is generously stored in the fetal liver, without a significant tendency to return from these stores to the maternal circulation.

Conclusions

A study has been carried out of the maternal-placental-fetal metabolism of carotene and vitamin A. This has revealed that:

1. An increase in maternal carotene led to an increase in both fetal carotene and fetal vitamin A.

2. An increase in maternal vitamin A, in and of itself, did not have a similar response in the fetal circulation.

3. Williamson's hypothesis that the transfer of vitamin A across the placenta was inversely proportionate to the fat content of the placenta could not be substantiated.

4. High values of fetal vitamin A and cholesterol were associated with statistical significance.

5. The carotene level in the placenta was higher than the level of vitamin A. In approximately two-thirds of the babies the carotene level of cord venous blood was higher than the carotene level of the cord arterial blood.

6. In the fetal liver the vitamin A level was always significantly higher than was the carotene level. The plasma levels of A in the fetal arterial and venous blood were invariably almost identical.

7. It is concluded that the principal transfer to the fetus takes place in the form of carotene, and that the fetal system converts the carotene to A, and stores it in high concentrations in the liver. Intrauterine vitamin A deficiencies would seem to result either from long-standing maternal deficiencies in carotene or from failures in the regulatory mechanism which controls fetal conversion of carotene to A.

The author wishes to express his sincere appreciation to Mrs. Helen Q. Keith for her technical assistance, and to Professor D. R. Whitney of the Department of Mathematics for the statistical analysis.

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THE CARDIAC PATIENT IN PREGNANCY

A Five-Year Survey

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MUCH has been written about this subject by those who have made detailed studies of the associated conditions, and there are on record excellent recommendations, rules, and regulations for the care of this group. It is felt that any statements of this nature made here would be useless repetition. But for purposes of comparison, our experience and results should be of some value and it is with this idea in mind that this report is being made.

Material

The period covered is five years, from Jan. 1, 1942, through Dec. 31, 1946, during which 13,908 patients were delivered and discharged from the Obstetrical Service of the University Hospital, Baltimore, Maryland. Of these, 88 were classified as having heart disease of varying severity. Ten were delivered twice in the five-year period, so that we actually treated 98 patients, an incidence of 0.71 per cent. This is considerably smaller than is generally reported, and may in part be due to the fact that the incidence of heart disease in this community is somewhat lower than in other centers.

TABLE I

CARDIAC CLASSIFICATION	1942	1943	1944	1945	1946	TOTAL
Class I	13	10	9	4	12	48
Class II	7	6	5	4	3	25
Class III	2	3	1	4	2	12
Class IV	7	0	1	4	1	13
Total	29	19	16	16	18	98
Patients delivered	2,991	2,960	2,960	2,312	2,685	13,908
Incidence	0.97%	0.64%	0.54%	0.69%	0.67%	0.71%

TABLE II

CARDIAC CLASSIFICATION	AVERAGE AGE (YEARS)	PARITY		PRIVATE	CLINIC	TOTAL
		PRIMIP.	MULTIP.			
Class I	25	20	28	23	25	48
Class II	23	12	13	8	17	25
Class III	30	3	9	5	7	12
Class IV	31	4	9	6	7	13
Total		39	59	42	56	98

TABLE III

CARDIAC CLASSIFICATION	AGE OF PATIENTS (YEARS)			
	15-24	25-30	31-40	41-45
Class I	18	15	13	2
Class II	19	2	4	0
Class III	2	7	3	0
Class IV	5	2	4	2

Tables I, II, and III give some pertinent data about the classification of the heart disease, the parity, and the ages of these 88 women. They require no particular comment.

Table IV is an effort to summarize the results of the 98 deliveries of the group. Many of the pertinent facts will be found here, which will be elaborated upon and further facts brought out later.

TABLE IV

SUMMARY	TOTAL	HOSPITAL SERV.		PRIVATE
		WHITE	NEGRO	
1. Number of patients discharged	101	28	33	40
2. Number of patients delivered and discharged (twins 2 sets)	98	27	32	39
a. Patients delivered of viable infants (twins 1 set)	92	26	31	35
b. Patients aborting (twins 1 set)	6	1	1	4
3. Maternal mortality	4	1	2	1
a. Rate per 1,000 live births	41	37	62	25
4. Number of viable babies born	93	27	31	35
a. Term	83	21	29	33
b. Premature*	10	6	2	2
5. Number of living babies	91	26	30	35
a. Term	81	20	28	33
b. Premature*	8	6	0	2
6. Number of stillbirths	2	1	1	0
a. Term	1	1	0	0
b. Premature*	1	0	1	0
7. Number of neonatal deaths	2	0	2	0
a. Term	1	0	1	0
b. Premature*	1	0	1	0
8. Total fetal mortality	4	1	3	0
a. Rate per 1,000 births	43	37	96	0

*A premature baby is one which weighs between 1,000 and 2,500 grams at birth.

The question of therapeutic abortion is one which has caused considerable discussion and one about which there appears to be marked difference of opinion among both obstetricians and cardiologists. Reports from well-organized and generally recognized clinics report an incidence of therapeutic abortion varying from zero per cent to a figure so high that it seems extremely radical. For example there is a report of one clinic in which more than 16 per cent of all the therapeutic abortions were done for this indication.

It is admitted that the risk of a pregnancy added to a severe heart disease is great and that these women would without doubt be better off if pregnancy had not occurred. But, faced with the fact of a pregnancy, it is difficult to decide in the individual case whether therapeutic abortion increases greatly the life expectancy. Individual cases should not be used to prove or disprove statements, but the history of one patient under the care of one of us is rather interesting in this regard.

A 35-year-old woman, para 1-0-0-1 was seen early in pregnancy with recommendations from two well-trained cardiologists that her pregnancy be interrupted because of Grade IV

heart disease (rheumatic). Her first pregnancy had been conducted without great difficulty and without decompensation. It terminated in delivery from below about 18 months prior to the onset of the present pregnancy. Since this delivery there had been 2 episodes of severe decompensation, from which recovery was quite prolonged. It was the opinion of the cardiologist who had watched her through her first pregnancy that her cardiac status had definitely worsened. A therapeutic abortion was done and the patient made an uneventful recovery, remaining in the hospital 14 days after operation. (This patient was treated after the period covered by this report.) About 3 months later, or when she would have been some 18 to 20 weeks pregnant, she developed a respiratory infection, with decompensation, and died. Had the pregnancy been allowed to continue, it would almost certainly have been considered a main contributing factor in her death.

In the five-year period under consideration pregnancy was interrupted once for heart disease, this being in a patient with an advancement to Grade IV, seen early in her pregnancy. The operation was done on the definite recommendation of the cardiac consultant, was followed later by tubal ligation, and was without incident. In this same period 21 therapeutic abortions were done for various indications, an incidence of 4.7 per cent of all therapeutic abortions being done for heart disease.

In order properly to evaluate this rather conservative policy as regards therapeutic abortion a complete follow-up report of these 88 patients should be available. Unfortunately this could not be obtained, since many of them belonged to the clinic group who moved frequently and without leaving forwarding addresses. Others were transients, living in Baltimore under war conditions, and returning to their homes later. If the 4 maternal deaths are studied from this angle it might be claimed that in one of them (No. 3 summarized below) death might not have occurred had the pregnancy been terminated in the very early weeks. On the other hand, it can be argued that if the patient had sought care early in pregnancy and had she been treated properly, she would most likely have had a successful termination of the pregnancy.

While it is our conviction that abortion is indicated only in rare instances and then only when done at the optimum time, we feel rather strongly that a number of these patients should have no further pregnancies, and a number of them are offered and accept sterilization.

These are summarized in Table V. The data presented here are not remarkable and require little comment. One fact of some interest is that the procedure accompanied section four times.

TABLE V. POSTPARTUM STERILIZATION

CARDIAC CLASS	TOTAL NO. STERILIZATIONS	TOTAL NO. IN EACH CASE	% OF STERILIZATIONS
Class I	6	48	12.5
Class II	3	25	12.0
Class III	7	12	54.5
Class IV	2	13	15.3

SOURCE	TOTAL NO.	POMEROY P.P.	ACCOMPANYING SECTION	X-RAY
White service	4	2	1	1
Negro service	4	4	0	0
Private	10	7	3	0

CARDIAC CLASS	ACCOMPANYING SECTION	WHITE	NEGRO	PRIVATE
Class I	1	0	0	1
Class II	1	0	0	1
Class III	0	0	0	0
Class IV	2	1	0	1

Abdominal delivery was considered necessary 7 times in this group of 88 women; however, heart disease itself was not among the indications. Contracted pelvis necessitated the operation in 2 instances, pre-eclampsia, breech presentation, and congenital anomalies of the vagina and cervix once each, while one was a post-mortem section. The final abdominal delivery was by laparotomy for rupture of a previous section scar. The treatment was repair of the rent and sterilization.

There has been a good deal of discussion between the cardiologists and the obstetricians as to the optimum time in the puerperium to sterilize these individuals. Were we always to follow the generally recommended procedure of waiting three to six months, many of our patients would not be sterilized. Either they would refuse to re-enter the hospital or they would again be pregnant. Therefore, it has been our general practice to observe these patients for two weeks after delivery, and if they show no evidence of decompensation to sterilize them at this time. If the patient happens to fall in the category of Class IV, this routine is abandoned and the three to six months' rule is enforced.

This routine has been in effect for longer than the five-year period being reported, and up to the present has caused neither mortality or decompensation. It should be added that in each instance the patient is evaluated by the cardiologist prior to operation and his consent obtained.

There did occur one instance in which the above precautions were not followed, the patient being sterilized on the third postpartum day. (See summaries of maternal deaths.)

Fetal Results.—There were 93 viable babies born in this series (one set of twins). Of this number 91 were born alive. The 2 stillborn infants were those of (1) a patient who died undelivered and upon whom a post-mortem section was done and of (2) a patient in whom the fetal heartbeat was absent prior to the onset of labor.

There were 2 neonatal deaths, one from prematurity, and one from a probable cerebral injury at birth. This gives us a total fetal mortality of 4, or a rate of 43 per 1,000 viable births.

Maternal Mortality.—There were 4 deaths among these 88 women or 98 pregnancies. On the former basis the rate is 4.42 per cent and on the latter 4.08 per cent. On the usual basis of live births, the mortality rate is 43.9 per 1,000. The over-all rate for the clinic for the same period was 2.13 per 1,000 live births. This indicates the seriousness of heart disease to the pregnant woman; in this report the risk appears to be more than 20 times as great.

A summary of these 4 deaths follows:

CASE 1.—L. W., No. 50549, a 41-year-old, para 4-0-0-4, was admitted to the hospital Feb. 25, 1942, in the last trimester of pregnancy, having been referred by her family physician because of hypertension, orthopnea, and blurring of vision. Her past history was negative for hypertension or symptoms of heart disease until the present pregnancy. She reported to her physician for the first time in this pregnancy about 2 months prior to admission to the hospital. We were told that her blood pressure at this time was 185 (diastolic not given). She was not seen again until the day of admission. When she entered the hospital her blood pressure was 206/126 and she presented the typical picture of severe hypertensive cardiovascular disease with pronounced decompensation. Under very vigorous treatment she gradually improved to the point where she was allowed out of bed for short intervals. On March 31, 1942, about five weeks after entering the hospital, she went into spontaneous labor and 1 hour and 20 minutes later delivered without assistance a full-term dead male child, weighing 3,150 grams. The patient withstood labor very well and did nicely for the first eleven days. However, on the twelfth postpartum day she suffered a cerebral accident, resulting in a right-sided hemiplegia. Death occurred two days later.

Comment: This is not in its strictest sense a death from cardiac disease, but is included because of the severe decompensation on admission. Is it a preventable death? One may well doubt that she had developed such a severe hypertensive disease during this pregnancy. Had the condition been recognized, and had she received proper treatment, including prevention of pregnancy, it might be that she would have lived for some years longer. The treatment at the hands of her family physician seems open to criticism. Certainly a patient as ill as she was when first seen deserved much more care and attention than she received. After admission to the hospital she appeared to have been treated rather well. Altogether it would seem that this was a preventable death.

CASE 2.—P. T., No. 67985, a 30-year-old, Negro, para 5-1-1-4, was admitted Dec. 10, 1943, from the outpatient department. Past history was negative from cardiac standpoint. A heart murmur was heard in the prenatal clinic and the patient referred to a cardiac consultant. Diagnosis: functional murmur. She was admitted with severe upper respiratory infection and apparent cardiac failure. The opinion of medical consultant was that the heart condition was probably on a syphilitic basis. Labor began spontaneously Dec. 12, 1943; a full-term living child was delivered spontaneously after a total labor of 4½ hours, with no analgesia or anesthesia. The patient died two hours post partum. No autopsy was performed. The apparent causes of death were diffuse bronchiolitis, severe toxemia from infection, and cardiac failure.

Comment: While not directly resonsible for the death of this patient, it must be admitted that the failure of the cardiac consultant to recognize the cause of the heart murmur when she was seen by him early in pregnancy was a contributing factor. Had everyone been aware of the true nature of the condition, she would have been watched more closely, and might have reported earlier with the respiratory infection. This can be only a postulation in this case, however, and it is likely that this would not be classified as a preventable death.

CASE 3.—L. M., No. 73346, a 23-year-old, Negro, para 4-0-0-4, was admitted to the medical service from the cardiac clinic June 30, 1944, because of severe decompensation. She gave a very vague history of swelling of the right knee as a child, otherwise her early medical history was noncontributory. The cardiac condition first became apparent in January of 1943, several months after the birth of her last child. She was admitted to the medical service July 21, 1943, with a diagnosis of rheumatic heart disease, Grade IV accompanied by decompensation and fibrillation. Under routine treatment there was gradual improvement and she was discharged Dec. 14, 1943. The last menstrual period was Dec. 15, 1943. She was followed in the cardiac clinic, but did not mention the possibility of pregnancy until the last visit on the day of admission. Decompensation was well established at this time. The usual treatment was instituted and it was planned that she would remain in hospital until after delivery. On July 26, 1944, after about one month of hospitalization, she complained of sudden shortness of breath and fell back in bed dead. By post-mortem section, a premature dead child, weight 2,268 grams, was delivered.

Autopsy showed scarring of mitral valve, chronic passive congestion.

Comment: While it is true that this patient should not have died at this time, it is difficult to place the blame on any one person. Had it been realized by the medical service when she was in the hospital in 1943 that she would become pregnant as soon as discharged, and had she been sterilized at that time, the result might have been delayed. Again, therapeutic abortion or more intensive treatment early in pregnancy might also have lengthened her life somewhat. The failure of the patient to report the pregnancy was probably a contributory factor.

If this is to be classified as a preventable death, it would appear that the responsibility rests largely with the patient herself.

CASE 4.—C. H., No. 13038, a 31-year-old, white, para 1-0-0-1, private patient, was admitted June 1, 1945, in active labor. Past history was positive for scarlet fever at age of 8 years, followed by joint involvement, and rheumatic fever at age 24. Her first pregnancy terminated at term 5½ years prior to admission. The heart disease was present at that

time and was considered to be Class II. The patient was seen early in present pregnancy when therapeutic abortion was considered and rejected as not being indicated. During pregnancy there were two episodes of rather marked dyspnea with blood-tinged sputum. Ten days before onset of labor fibrillation began and patient was started on digitalis, but was allowed to remain at home. Labor was easy and short. She was delivered under open drop ether. Her postpartum condition was good except for moderate increase in pulse rate. She was seen by the cardiac consultant on June 3, 1945, and he agreed to sterilization the following day. This was carried out under open drop ether anesthesia, and twenty-four hours after operation the patient developed acute heart failnre and died forty-eight hours later.

Comment: Without question this was a preventable death, the burden being upon both the obstetrician and the cardiac consultant. It is difficult to understand the two major lapses in the care of this patient. First, no plans appear to have been made to hospitalize her routinely some two to three weeks prior to the estimated date of confinement, and this simple but valuable precaution was not taken when fibrillation began. Second, sterilization on the third day of the puerperium was in direct contradistinction to all modern teachings and practices. The cardiac consultant should not have agreed to the operation, and the obstetrician should not have performed it even though he did agree.

Conclusions

While this report is presented primarily for purposes of comparison, it is difficult not to make some comment, particularly upon facts not brought out above. Most certainly we are not at all proud of the picture as printed and feel that a better job could have been done by everyone concerned.

Among the outstanding errors in handling the cases should be listed:

1. Failure properly to diagnose and evaluate the cardiac status. This eror was repeated a number of times.
2. Failure to impress upon the patient the real seriousness of her condition and to secure her full cooperation.
3. Failure to hospitalize at the first sign of decompensation and to continue hospitalization until well after delivery.
4. Failure to admit all cardiacs routinely to the hospital some two to three weeks before term.
5. The use of inhalation anesthesia rather than regional or local.
6. Too early ambulation and too short hospitalization post partum.

In defense it might be stated that the period covered by this report was during the war, when personnel was lacking and demand exceedingly heavy. The house officers were frequently changed and facilities for their instruction were none too good. Time was a most acute factor.

What lesson may be learned from this study? Probably the principal one is that the cardiac patient during pregnancy is most unpredictable and requires extremely close supervision, careful evaluation, and prompt treatment.

TRUE TOXEMIA OF PREGNANCY OCCURRING BEFORE THE THIRD TRIMESTER: REPORT OF THREE CASES AND REVIEW OF THE LITERATURE*

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THE twenty-fourth week of pregnancy has been adopted as a dividing line between pre-existing hypertension and true toxemia of pregnancy because the latter seldom, if ever, appears before that time.[9] We have encountered, within the last three years, what we believe to be 3 cases of true toxemia of pregnancy occurring before the third trimester. The difficulties encountered in the management of these patients have prompted us to review our experience and to consider briefly the English literature relative to early toxemia of pregnancy.

Kosmak,[7] in 1922, stated that although the toxemias of pregnancy, as a rule, were associated with the later months of pregnancy cases have been repeatedly observed during the first half of pregnancy. He cited a case of convulsions occurring in the fourth month of pregnancy in which necropsy showed severe hemorrhage, chronic nephritis, and characteristic eclamptic changes in the liver. He also commented on E. P. Watson's case of a primigravid woman, aged 25 years, in which generalized edema and headache developed gradually and finally coma occurred after severe and typical eclamptic convulsions in the fifth month. The urine of this patient contained an excessive amount of protein and many granular casts. Vaginal section was done and a twin pregnancy was terminated.

Füth,[6] in 1928 reveiwed Ebeler's work reported in 1911. Ebeler had gathered 55 cases of early eclampsia from the literature. Four of the patients had been seen in the Cologne Clinic alone. Thirty of these cases were presented with a reasonable degree of completeness and the remaining cases by summary and operative findings only. A complete protocol was available in only 2 cases.

Füth's case was that of an illegitimately pregnant primigravid woman who had acute toxemia in the fourth month of pregnancy. The difficulties in differential diagnosis were great, and drug intoxication, criminal abortion, and appendicitis were included among the early diagnoses. The patient died approximately five hours after her first convulsion. Therapeutic agents and maneuvers utilized in this case were the administration of morphine and lobeline, renal decapsulation, and lumbar puncture. The uterus apparently emptied itself spontaneously. Necropsy revealed subacute glomerulonephritis with degenerative parenchymal changes in the fashion of nephrosis and distinct, although minimal, changes of eclampsia in the liver. Füth stated that of the 56 cases of early eclampsia known to him, 11 had resulted in death.

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*Read at a meeting of the Minnesota Obstetrical and Gynecological Society, Rochester, Minn., April 29, 1950.

DeLee,[3] in the 1928 edition of his standard textbook, stated that toxemia of pregnancy most commonly occurs in the last three months of pregnancy, but did occur as early as the tenth week in a case of his own. He referred to fatal cases in which toxemia had occurred in the third, fourth, and fifth months of gestation.

Porter,[10] in 1934, referred to Shearer, who warned that many cases of supposed early toxemia of pregnancy were examples of nephritis. Porter presented a fatal case of his own, that of a woman, 43 years old, in the fifth lunar month of pregnancy. At necropsy evidences of chronic cardiovascular change and chronic renal disease were found. Stander,[12] in 1938, mentioned the report of Bourne in which he described a case of true toxemia of pregnancy occurring in the twenty-fourth week of pregnancy.

Dieckmann,[5] in 1941, emphasized that convulsions due to eclampsia are infrequent before the thirtieth week of pregnancy and are extremely rare in the first half of pregnancy and that the number of authenticated cases proved at necropsy is small. Hermann's series of 3,260 cases of eclampsia was cited. The incidence of eclampsia before the twenty-eighth week of pregnancy was 0.8 per cent. Dieckmann stated that only one of his patients had had eclampsia before the thirtieth week of gestation and that pre-eclampsia had not occurred before the twenty-fourth week. Dexter and Weiss,[4] in 1941, commented that toxemia of pregnancy had occurred in their series as early as the twenty-fourth week of gestation. Beck,[2] in 1942, stated that statistical analyses showed that true toxemia of pregnancy occurred before the fifth month in about 1 in every 500 cases of this condition. He also reviewed the opinion that when pre-eclampsia or eclampsia is encountered early in gestation it is usually a complication of hydatidiform mole. A review of 306 cases in Beck's series showed that toxemia of pregnancy occurred in 1 case in the second to third month and in 13 cases in the fifth to sixth months of pregnancy.

Arnell,[1] in 1945, presented a series of 142 cases of eclampsia without a maternal death and stated that the earliest in pregnancy that this condition had occurred in his series was the twenty-sixth week. His series also included cases in which it occurred in the twenty-eighth and thirtieth weeks. Stander,[11] in 1945, referred to Zweifel's case in which toxemia had developed in the third month. Stander emphasized again the fact that reports of eclampsia in the first half of pregnancy or more than twenty-four hours after delivery should be regarded with skepticism and that careful investigation usually would indicate that the convulsions were of some other origin.

Whitacre, Loeb, and Chin,[13] in 1947, discussed 100 consecutive cases of eclampsia observed in Peiping, China, and noted that in 2 of these eclampsia had occurred before the sixth month of pregnancy and that in 1 of a group of 100 consecutive cases from Memphis, Tenn., it had occurred before the sixth month.

A case[8] presented at the staff conference of the Margaret Hague Maternity Hospital in September, 1949, is of interest. The patient, para ii and 29 years of age, was admitted in the twenty-seventh week of her third pregnancy. She gave a history of having had two convulsions at home and of having "vomited everything" for the past two or three weeks. Hypertension and minimal proteinuria were present on entry. The diagnosis of eclampsia made on admission was abandoned when the initial blood chemical studies demonstrated severe alkalosis with hypochloremia, probably secondary to prolonged vomiting. McCarthy, in discussing this case, referred to a patient who, after sixty convulsions at home, died in the twenty-fifth week of gestation, a few hours after admission to the Margaret Hague Maternity Hospital in 1937. The editor in commenting on this report cited a case in the same hospital in which the patient had

eclampsia at the end of the first trimester of pregnancy. In this particular case the eclampsia was associated with hydatidiform mole. We have not reviewed these cases.

Report of Cases

CASE 1.—The patient, aged 24 years, gravida i, para 0, who had been married for three years, registered for prenatal care on July 13, 1949. Her last menstrual period had been March 24, 1949, and the expected date of confinement was Dec. 31, 1949. Her medical history was noncontributory except that she had had scarlet fever at the age of 13 years with no apparent sequelae. She had had a tonsillectomy in February, 1946, and biopsy of some enlarged left cervical lymph nodes in May, 1949, had proved them to be inflammatory. Menses which had begun at 10 years of age, occurred at regular intervals of twenty-eight to thirty days, and lasted for five days with moderately heavy, painless flow. Results of general physical examination were negative except for right cervical and left axillary adenopathy. Her weight was 104 pounds (47.2 kg.) and her normal weight was recorded as 105 pounds (47.6 kg.). The pelvis was adjudged to be small from an obstetrical point of view and pelvimetry was planned for a later date. Her blood pressure was 126/78.

The patient was next seen on Aug. 15, 1949, at which time her blood pressure was 144/82 and when rechecked by the examining physician was found to be 150/90. Ankle edema was graded 1+ (on a basis of 1 to 4 in which 1 is the least and 4 is the greatest amount). The patient had felt fetal movements and was well except for paresthesia of both hands.

The uterine fundus was 1 fingerbreadth below the umbilicus. The patient had gained 6¾ pounds (3.0 kg.) in the preceding month and now weighed 110¾ pounds (50.2 kg.). A salt-free diet and 1 mg. of stilbestrol three times a day were prescribed and she was told to return in four days.

She returned four days later, on August 19. Her blood pressure on two determinations then was 172/130 and 160/90. She had gained 2 pounds (0.9 kg.) and had had vague crampings in the lower part of the abdomen for four days. The patient was advised to stop work immediately and ½ grain (0.032 Gm.) of phenobarbital three times a day and 1½ grains (0.1 Gm.) of sodium propylmethylcarbinylallylbarbiturate (Seconal) at night were prescribed. Determinations of blood urea nitrogen and serum sulfate and examination of the ocular fundi and withdrawal of a catheterized specimen of urine were ordered immediately.

The patient called the following morning while the laboratory tests were being performed and said that she was having considerable upper abdominal pain. She was ordered to the hospital by telephone.

When she was admitted to the hospital at 4 P.M. on August 20, she complained of pain in the upper part of the abdomen and beneath the lower part of the sternum of twenty-four hours' duration. Her blood pressure was 170/90, the pulse rate was 84 beats per minute, and the temperature was normal. Epigastric tenderness was observed. The consultant's note read in part: "Aside from the period of pregnancy [fifth month] the story is typical of pre-eclampsia." Routine management of toxemia consisting of a salt-free diet, sedation, rest in bed, careful measurement of intake and output of fluids, frequent readings of blood pressure and administration of hypertonic solution of glucose was instituted.

At 10:40 A.M. on August 22, the patient lapsed into semistupor with facial grimaces and stertorous breathing. The blood pressure was 150/90. When she regained consciousness she complained of severe headache. Another convulsion occurred shortly. A dose of 7½ grains (0.5 Gm.) of pentobarbital sodium was given intravenously at once and the aforementioned therapy was intensified. Examination of the retinal arterioles showed generalized narrowing, minimal to grade 1, with focal constrictions. There was no retinitis or sclerosis.

Examination of the ocular fundi in the morning of August 23 showed no essential change from the preceding day. The urinary output was adequate on this day and on

the following day. On August 25, the urinary output was approximately 700 c.c. and the level of both systolic and diastolic blood pressure seemed to have risen. On August 26, additional spastic focal constrictions were noted in the retinal arterioles in the regions of both optic discs.

On August 27, after seven days of hospitalization because of the persistent hypertension and albuminuria and evidence of progressive vascular damage as demonstrated by funduscopic examination, abdominal hysterotomy was performed. As nearly as could be calculated by dates, the pregnancy at that time was of approximately twenty-two weeks' duration.

The postoperative course was completely without untoward event. The blood pressure on September 5 was 112/75 and on September 6, 116/70. Findings in an excretory urogram on September 4 were regarded as normal except for a possible discrepancy in the size of the kidneys, the right kidney being larger. The patient was dismissed from the hospital on September 6. The patient was readmitted on September 8 and remained until September 15 because of pneumonitis in the lower lobe of the right lung with associated pleurisy. This process cleared without further trouble.

This patient was again hospitalized Jan. 11 to 20, 1950, because of pain in the right lower quadrant of the abdomen. Appendectomy was performed. At the time of this operation leakage from a corpus luteum cyst of the right ovary was observed. When she was last seen in March, 1950, the cardiovascular renal status of this patient was regarded as essentially normal.

CASE 2.—A primigravid woman, 33 years old, with no previous history of hypertension or nephritis, entered the hospital on Feb. 11, 1950, because of headache, vertigo, and blurred vision. The history was obtained from the patient's husband. Her last menstrual period had occurred on Aug. 31, 1949. She was examined by the physician in her home locality in December, 1949. Results of urinalysis, routine blood tests, and blood pressure were within normal limits. On Feb. 2, 1950, she began to notice swelling of the ankles. Urinalysis and blood pressure on February 3 showed normal conditions. She returned to her physician on February 9 because of severe headache and vertigo. Her systolic blood pressure was 170 mm. of mercury on this day, and urinalysis showed albuminuria, grade 4. On February 10, the systolic blood pressure was 210 mm. and the urinalysis again revealed albuminuria, grade 4. She was then referred to the clinic and hospitalized immediately.

The diagnosis on admission was fulminating toxemia of pregnancy. The gestation was estimated to be of twenty-one and one-half weeks' duration. The blood pressure on admission was 210/112 mm. and there was generalized edema of the body, grade 2+ and edema of the legs, grade 3. Fetal heart tones were not audible. The routine management for pre-eclampsia was instituted. The ophthalmologist observed generalized narrowing of the retinal arterioles, grade 1+, with scattered focal constrictions. A superficial retinal hemorrhage and also a small choroidal hemorrhage were noted in the left eye. This consultant felt that the ophthalmoscopic picture was that of toxemia of pregnancy. The chemical constituents of the blood were only slightly abnormal on admission. It was considered that in all probability hysterotomy would be necessary as the prospect of carrying the patient to the period of fetal viability, if, indeed the fetus still lived, seemed hopeless. However, it seemed best at that time to attempt to stabilize her condition with medical measures. During the first forty-eight hours of hospitalization, a rather gratifying diuresis was obtained; the output was 3,950 c.c. in one twenty-four-hour period. The blood pressure was not, however, significantly altered.

On February 13, in spite of heavy sedation, the blood pressure rose suddenly to 210/142 and the patient had a severe convulsive seizure. The urine at this time was grossly bloody. A period of almost complete anuria followed, and in the next few days the patient had a total of nine convulsive seizures. Hypertonic solution of glucose, given intravenously, estrogens given intramuscularly, and barbiturates given intravenously were the principal measures employed. On February 15, renal function improved rather

markedly, 4,200 c.c. of urine were excreted in a period of twenty-four hours and the blood pressure decreased to 170/120 mm. Continuous caudal anesthesia had been instituted earlier in that day. However, it was the opinion of the attending obstetrician that the diuresis had actually begun before the caudal anesthetic was started. It was decided that the time for abdominal hysterotomy was at hand, and this procedure was undertaken on Feb. 16, 1950.

The improvement in the patient following hysterotomy and after the resolution of a small peripheral right pulmonary embolus was rapid. Funduscopic examination March 10 showed complete disappearance of the hemorrhages. The generalized narrowing of the arterioles still persisted. The patient returned directly to her home on March 11, 1950. Blood pressure on this day was 130/80 mm. and examination of the urine revealed a rapidly decreasing degree of albuminuria.

CASE 3.—A primigravid woman, 25 years old, was admitted to the hospital on Oct. 30, 1947. Her presenting complaints were pain in the epigastrium, elevated blood pressure, diplopia, and edema of the face and about the eyes of three to four days' duration. The patient had no history of albuminuria or hypertension. The menarche had occurred at 11 years of age, and the menses had always been normal. The last menstrual period had occurred on May 21, 1947.

Three weeks prior to admission the patient stated that "influenza" had developed. This illness consisted of generalized arthralgia, malaise, headache, and vomiting. A satisfactory recovery ensued. There was no particular sore throat with this episode. One week prior to entry the patient thought that she again had influenza and the complaints mentioned on admission developed in progression from this. There was no fever.

Physical examination on admission revealed a blood pressure of 170/110. The pregnancy was estimated to be of twenty-one weeks' duration. Urinalysis showed albuminuria, grade 4, many casts and an occasional erythrocyte. Examination of the ocular fundi showed generalized narrowing of the retinal arterioles, grade 1 to 1+, with no definite papilledema. The ophthalmologist commented that he had not seen this picture in ordinary acute glomerulonephritis and that it resembled that seen in eclampsia.

On Nov. 1, 1947, the diagnosis of toxemia of pregnancy was still more seriously considered since there were no erythrocytes to be seen in the urine and intense albuminuria and pretibial pitting edema were present. Palsy of the third cranial nerve was noted, and the neurologists postulated cerebral angiospasm as the most probable cause.

By November 6, it seemed that although some improvement in the clinical course was noted, the patient was proceeding with the pregnancy at great risk, and there was so small a chance of delivering a viable child that interruption of the pregnancy seemed wise. Slight increase in the narrowing of the retinal arterioles was observed on this day. Accordingly, vaginal hysterotomy was carried out on November 10. The postoperative course was entirely without untoward event. By November 13 the diplopia had cleared.

At the time of the patient's dismissal, the blood pressure was 130/90; the albuminuria had reduced itself to grade 1 and there was definite clearing of the retinal angiospasm. Examinations in March and June, 1948, showed no albuminuria nor edema. Residual narrowing of the retinal arterioles and some evidence of lability of blood pressure were still noted. The chemical studies on the blood did not yield particularly striking results in this case and will not be presented in detail. There was, however, a decrease in the value for serum sulfates from 5.4 mg. per 100 c.c. at the height of the illness to 3.6 mg. in March, 1948. Results of urinalysis performed in March, 1950, were completely normal. The blood pressure at this time was 144/90.

We do not regard this case as so definite an example of true toxemia of early pregnancy as the preceding cases because we do not have proof of the normalcy of the patient's kidneys prior to the gestation under consideration. Such normalcy however, is strongly suggested by the evidence.

Summary

We have reviewed the English literature relating to early toxemia of pregnancy and have presented our own experience with this interesting complication. It is important for the obstetrician to recall that true toxemia may occur before the last trimester. It is also important to realize that the diagnosis of pre-eclampsia and eclampsia in the early months of gestation is hazardous. The obstetrical diagnostician must demand that there be no evidence of pre-existing cardiovascular or renal disease, and the diagnosis would be substantiated if the signs and symptoms of toxemia cleared rapidly and completely with the termination of pregnancy. However, this latter criterion cannot be an absolute requisite for in many cases true toxemia occurring in the last trimester of pregnancy leaves the patient with residual cardiovascular renal damage. It is, perhaps, a defect of our presentation that we have not followed these patients for a longer period. However, it has seemed to us that at least two of these cases, and possibly the third, have been as definitive examples of this entity as we might hope to discover.

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THE VALIDITY OF VAGINAL SMEAR DIAGNOSIS IN CARCINOMA IN SITU OF THE CERVIX*

A Report of 60 Cases†

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IN THIS study of 60 cases of carcinoma in situ of the cervix, we wished first to determine the inherent ability of the vaginal smear to reveal the presence of such early malignancy; second, to assess our accuracy in discovering the malignant cells; and third, to consider the usefulness of the technique as applied to our clinic.

Material

During the period of three and one-half years covered by this study, 11,871 vaginal smears from 9,748 gynecologic patients were examined. A correlation between vaginal smear and tissue diagnosis in the first 1,045 cases to be examined in this manner has been previously reported by Isbell and associates.[1] The 60 cases of cervical carcinoma in situ under discussion are 15 per cent of a total of 398 cases of malignancy examined by vaginal smears during these years.

In 42 cases a vaginal smear was obtained before the histologic diagnosis was made by biopsy or hysterectomy. In the remaining 18 cases a histologic diagnosis was made before the initial smear was obtained. Thus 42 smears were definitely "unknowns" when interpreted, and, whenever possible, the smears from the remaining 18 patients were examined without knowledge of the histologic diagnosis. In each case only the initial smear diagnosis was utilized for this paper.

The vaginal smears were obtained by aspirating fluid from the posterior vaginal fornix and making a thin spread of the secretion on a single glass slide. The smear was then fixed immediately and stained according to a modification‡ of the Papanicolaou technique. Seven different readers have been responsible

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†Included in this study are 29 cases previously correlated with the vaginal smear and reported by Younge, Hertig, and Armstrong.[2]

‡The smears before drying are fixed for 15 minutes in a solution of equal parts of 95 per cent alcohol and ether. (If the slides are to be mailed, the smears are removed from fixative and allowed to dry. No glycerin is used.) The slides are then rinsed successively in 80 per cent, 70 per cent, and 50 per cent solutions of alcohol in distilled water, followed by distilled water alone. The smears are then stained for one and one-half to two minutes in a mixture of equal parts of Harris' hematoxylin and distilled water, thoroughly rinsed in tap water, and then placed for one minute in a 3 per cent solution of ammonium hydroxide in 70 per cent alcohol. The slides are then rinsed successively in two changes of 70 per cent alcohol, followed by 80 per cent and 95 per cent alcohol. They are then stained for three-fourths of a minute in OG-6, rinsed in two changes of 95 per cent alcohol, stained for one and one-half minutes in EA-50, and then rinsed in three changes of 95 per cent alcohol followed by absolute alcohol. The smears are placed in xylol and allowed to remain for a few minutes before they are mounted in Permount or Canada balsam. (Either methyl or ethyl alcohol may be used.)

for the smear diagnoses, two-thirds of which have been made by one of us (R. R. A.). The cytologic criteria for the diagnosis of invasive and preinvasive squamous carcinoma of the cervix have been fully described by other workers. We find, however, that malignant cells occur with less frequency in cases of preinvasive carcinoma than in those of more advanced cervical tumors, and are often accompanied by abnormal precornified squamous cells with markedly enlarged but otherwise normal nuclei. These atypical anaplastic cells occurred in more than 60 per cent of these cases, although they themselves are considered benign.

The microscopic examination of all tissue submitted was the sole responsibility of one of the authors (A. T. H.) who employed the histologic criteria of this disease previously described. It should be emphasized, however, that surface malignancy extending into the lumina of intact cervical glands is considered preinvasive until definite stromal involvement can be demonstrated.

Results

In an attempt to determine the highest possible accuracy of cytologic diagnoses, two of the authors (R. R. A. and R. E. J.) have reviewed all smears originally diagnosed as benign. The results of this review are reported as "Review Diagnoses" in Tables I, II, and III.

Table I. Vaginal Smear Diagnoses in 60 Cases of Carcinoma in Situ

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
42	18	70%	49	11	82%

Table II. Vaginal Smear Diagnosis in 24 Cases of Carcinoma in Situ With Surface Malignancy Only

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
13	11	54%	17	7	71%

Table III. Vaginal Smear Diagnosis in 36 Cases of Carcinoma in Situ With Surface Malignancy Plus Gland Involvement

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
29	7	81%	32	4	89%

In Table I is shown the correlation of the tissue diagnosis with the original cytologic diagnosis of the initial smear in each case. Also shown is the actual occurrence of neoplastic cells in these 60 vaginal smears as found on review of our false negative slides.

Thus by routine examination of the smears, we were able to diagnose malignancy in 42 of the total 60 cases, or 70 per cent, but on re-examination of the 18 false negative smears, malignant cells were discovered in seven additional cases, three of which each contained only two tumor cells. Therefore, malignant cells were eventually found to occur in 49 cases, or 82 per cent.

The difference between the original and review percentages reveals the difference between the accuracy in this laboratory of cytologic diagnosis of early cervical cancer, 70 per cent, and the potential accuracy inherent in the method itself, 82 per cent. The latter figure indicates what we consider to be the ultimate diagnostic possibilities of the vaginal smear when applied as a screening procedure in search of early cervical cancer in gynecologic patients.

As shown in Tables II and III, there is a striking contrast in the accuracy of smear diagnosis in cases with only surface malignancy as compared to that in the more advanced preinvasive lesions showing involvement of the cervical glands.

In 24 cases of carcinoma in situ showing only surface changes, we were able to diagnose malignancy on the first smear examination in only 13, or 54 per cent. (These figures are comparable to the results in the 31 cases reported by Younge and co-workers.[2]) Of the remaining 36 cases in which tumor was found to extend into the glands, 29 cases, or 81 per cent, were correctly diagnosed on first examination. These findings may be explained in part by the theory that cellular exfoliation may be enhanced by the normal secretory activity of the involved glands not completely obstructed by tumor, as well as by the fact that glandular involvement is a manifestation of a later stage of the disease. Seven cases in this series had no positive vaginal smears when repeated attempts were made.

Age and Symptoms

The average age of these patients was 35.2 years, and is somewhat lower than that reported by others, including the larger series of 135 cases from this clinic, in which the average age was found to be 38 years.[2] The oldest patient was 59 years, and the youngest 22 years of age. Fifteen, or 25 per cent, of the total number were found to be under 30. Only 20 of the 60 patients in this series had some form of abnormal vaginal bleeding. Of the remaining patients, 20 had leucorrhea or slight vaginal discharge, and 20 had no signs or symptoms referable to the genital tract. Approximately 50 per cent of the cervices were described on examination as eroded, lacerated, or hypertrophied, but only 9 per cent were found to bleed easily and hence were considered suspicious of having malignancy.

The Clinical Significance of the Positive Vaginal Smear

In the outpatient department of this hospital vaginal smears have proved useful not only as a routine screening procedure, but also as a method providing close follow-up for patients with questionable early malignancy of the cervix.

With few exceptions, the presence of malignant cells in a vaginal smear means that carcinoma is present somewhere in the genital tract. If one should arbitrarily assume that even in the absence of clinical symptoms and signs, the positive smear is indicative of early cervical carcinoma, should the patient be submitted to classical treatment of the disease? That a positive smear alone does not always justify definitive cancer treatment is shown by the occasional disappearance of malignant cells in vaginal smears following such procedures as simple biopsy or cauterization of the cervix. We have in our series three such instances in which the entire malignant area apparently was removed completely by cervical biopsy. An example of this is reported in Case 38. Four additional cases of carcinoma in situ were apparently destroyed by cauterization (e.g., Case 6); in two others, by cervical conization (as in Case 46), and in one patient the cancer apparently disappeared during the course of her pregnancy (Case 18).

CASE 38.—This patient, a 25-year-old white woman, para ii, was first seen on Aug. 31, 1948, complaining of a bearing down sensation in the pelvis, hypermenorrhea, and hemorrhoids. Her last delivery had occurred five months prior to admission. Examination revealed hemorrhoids, rectocele, cystocele, lacerated perineum, and a deeply lacerated and eroded cervix. A vaginal smear was positive for carcinoma. Two weeks later a second vaginal smear was obtained followed by curettage, biopsy, and cauterization of the cervix. The smear was again positive and examination of the tissue showed squamous carcinoma with

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TABLE III. VAGINAL SMEAR DIAGNOSIS IN 36 CASES OF CARCINOMA IN SITU WITH SURFACE MALIGNANCY PLUS GLAND INVOLVEMENT

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very early invasion. A complete hysterectomy was performed on Sept. 18, 1948, 3 days later, at which time the entire cervix was divided into 7 blocks and 11 microscopic sections were examined. No carcinoma was found.

CASE 6.—This patient, a 31-year-old white woman, was seen on Aug. 28, 1946, complaining of intermenstrual spotting. The cervix was described as hypertrophied and markedly eroded with one tiny black area suggesting endometriosis. The biopsy showed anaplasia. Vaginal smears taken Sept. 25, 1946, and Oct. 17, 1946, were positive, and cervical biopsies on the same dates showed carcinoma in situ. The cervix was cauterized on Oct. 24, 1946, because of the patient's request for conservative treatment. On Jan. 2, 1947, four months after admission and two months after treatment, the cervix was found to be normally epithelized and a smear and biopsy were negative. The patient was last seen March 17, 1949, two years after treatment, at which time vaginal and cervical smears and a biopsy were negative.

CASE 46.—This patient, a 38-year-old woman, was seen on Feb. 1, 1949, with a chief complaint of irregular flowing. Her history and pelvic examination were not significant, the cervix being described as smooth, well epithelized, and showing no evidence of carcinoma or erosion. A vaginal smear was reported as being definitely positive for carcinoma. Two weeks later curettage and conization of the cervix were performed that left a crater 2.5 cm. in diameter and 1 cm. deep. The histologic findings were mid-proliferative endometrium and carcinoma in situ of the cervix with gland involvement. Because there was some question of the extent of the tumor in the cervical canal, a cervical amputation was performed 3 days later. No evidence of residual tumor was found in 14 microscopic sections cut from nine blocks of cervical tissue.

CASE 18.—This patient, a 28-year-old woman, was first seen Dec. 12, 1946, with complaints of abdominal cramps and slight leucorrhea. The cervix was inflamed and eroded and a biopsy showed anaplasia. A vaginal smear taken a week later was negative. On April 17, 1947, the patient was found to be 10 weeks pregnant. A cervical biopsy of a Schiller positive area showed carcinoma in situ and a vaginal smear was positive. The patient refused operation and was followed during her pregnancy with monthly vaginal smears. The smears remained positive until the sixth month of gestation when on July 24, 1947, a negative smear was obtained. The vaginal smear thenceforth remained negative. The patient had an uneventful delivery on Oct. 24, 1947. She has been examined in the clinic regularly for two and one-half years, and when last seen on Sept. 22, 1949, the cervix was found to be slightly everted. A Schiller test, two cervical biopsies, and a vaginal smear all were negative at this time.

For these reasons and the fact that false positive diagnoses, however rare, are not impossible in any cytology laboratory, we take issue with Ayre[3] who states while enumerating the values of cytologic tests: "One stage of an operation is eliminated in a suspicious case. Radium is inserted at the time of biopsy without necessitating delay for the biopsy result. The confidence to permit such a procedure must be built up through experience."

We believe that because this method of cancer diagnosis is still being evaluated in regard to the less advanced lesions, it would seem unwise (and we believe therapeutically unnecessary) to destroy such early tumors before their nature and extent are established.

Of our 60 cases of cervical carcinoma in situ, 12 were clinically unsuspected and therefore discovered by routine vaginal smears. All but one of these cases (reported by Younge and associates[2]) have been found in the last two years. Nine of these 12 cases were confirmed by biopsy or by specimens excised by conization prior to hysterectomy. In two instances hysterectomy was performed because of profuse flowing before the positive smear diagnosis was confirmed by

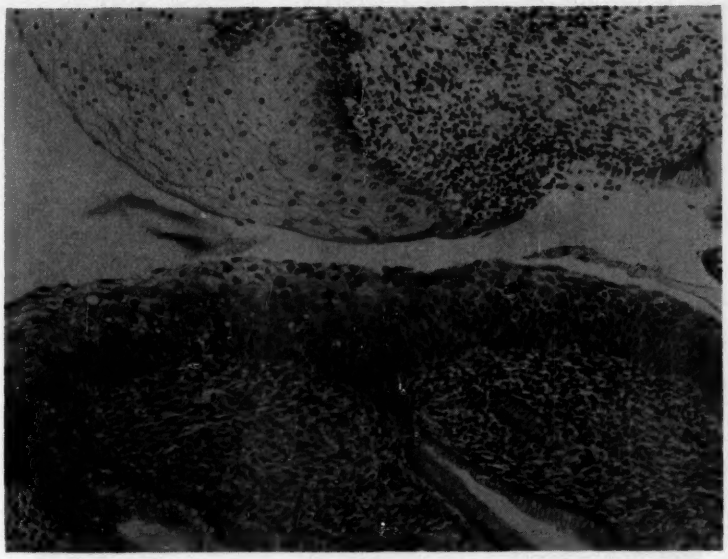

Fig. 1 (Case 46).—This picture shows a cervical gland with extension of normal epithelium on upper side. The epithelium on the lower side shows the transition of anaplastic epithelium to carcinoma in situ which is extending deeper into the same gland and is beginning to extend into two of its branches. There is no actual stromal invasion.

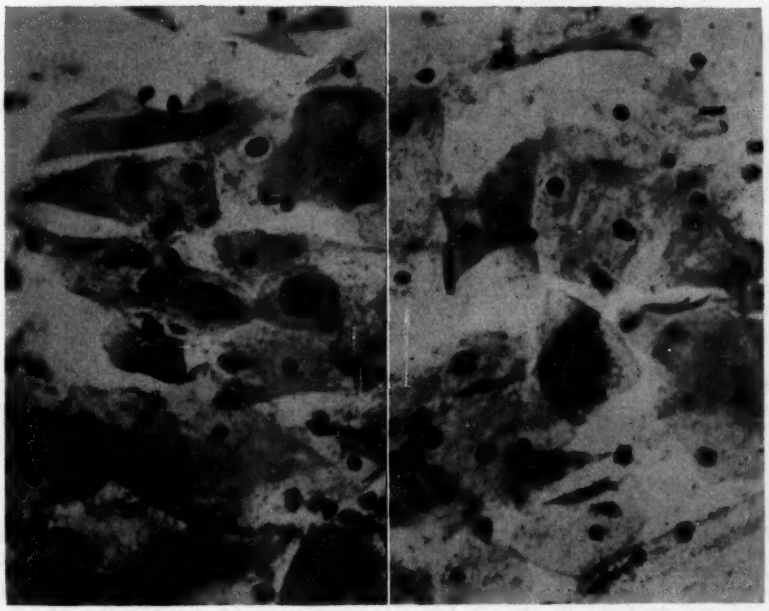

Fig. 2. Fig. 3.

Fig. 2.—Same case as Fig. 1. Two malignant squamous cells with large, irreguiar, and hyperchromatic nuclei.

Fig. 3.—Same case as Fig. 1. Single, large, anaplastic squamous cell. Nucleus is enlarged but smooth in outline with slightly increased chromatin. This cell type appears in over 60 per cent of cases of carcinoma in situ.

tissue examination. The remaining case (No. 51) was that of a patient who had two smears reported as definitely positive for carcinoma, and had a hysterectomy after two negative biopsies, yet carcinoma in situ was found in the extirpated cervix.

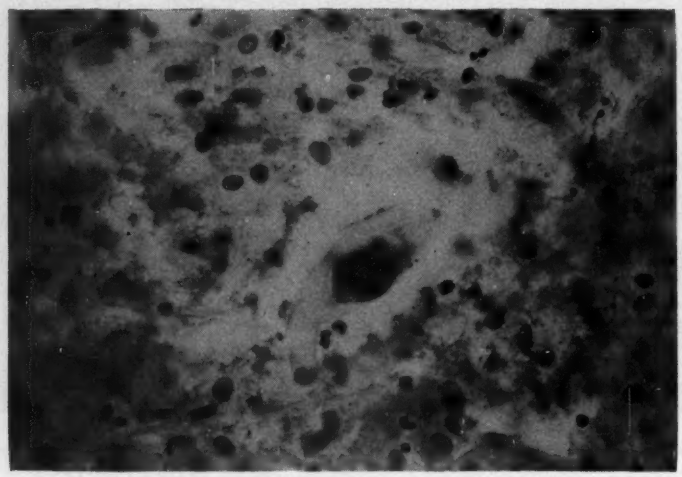

Fig. 4 (Case 18).—Large multinucleated tumor cell with abundant cytoplasm and bizarre outline. Such cells appear frequently in carcinoma in situ.

CASE 51.—This patient, a 38-year-old white woman, para ii, gave a past history of sterility of 4 years' duration and an operation for kidney stones in 1936. There was no history of vaginal bleeding, and on March 3, 1949, the cervix appeared hypertrophied with leucoplakia on the posterior lip, covering an area 1 cm. by 0.5 cm. A vaginal smear taken at this time was reported as being definitely positive for carcinoma, and a cervical biopsy showed leucoplakia with marked anaplasia. Both procedures were repeated on April 11, 1949, and the vaginal smear was again definitely positive, while the biopsy of the cervix showed only leucoplakia. On April 22, 1949, an attempt to curette the cervical canal was unsuccessful and a complete hysterectomy was done. The microscopic diagnosis was carcinoma in situ of the cervix with glandular involvement. No tumor was found at the external os, but one was found to extend up to the internal os involving almost the entire length of the endocervical canal.

Eleven of the 12 cases discovered by smear were treated eventually by complete hysterectomy or trachelectomy, and one patient with a confirmatory tissue diagnosis of carcinoma in situ of the cervix is still being followed in the clinic.

When a positive smear diagnosis is encountered, it is the practice to recall the patient to the clinic and every attempt is made to confirm the diagnosis. Needless to say, it is impossible to disprove absolutely a positive smear diagnosis. If a patient is found to have positive vaginal smears and yet only negative findings result from multiple biopsies and curettage, she is asked to return to the clinic at regular semiannual intervals for repeated smears and biopsies.

In the presence of a doubtful vaginal smear, more definitive information may be obtained by making smears of endocervical or endometrial secretions since these occasionally contain larger numbers of malignant cells than are found in the vaginal desquamate. Whenever possible, all three types of smears should be made on each gynecologic patient to provide the greatest opportunity for diagnosis. Unfortunately, most cytology laboratories find this pro-

cedure economically impossible for routine screening of a large number of patients, and must rely on the use of vaginal smears alone to provide the diagnosis, using the more specific types of smears for aid in suspicious cases.

Fig. 5.

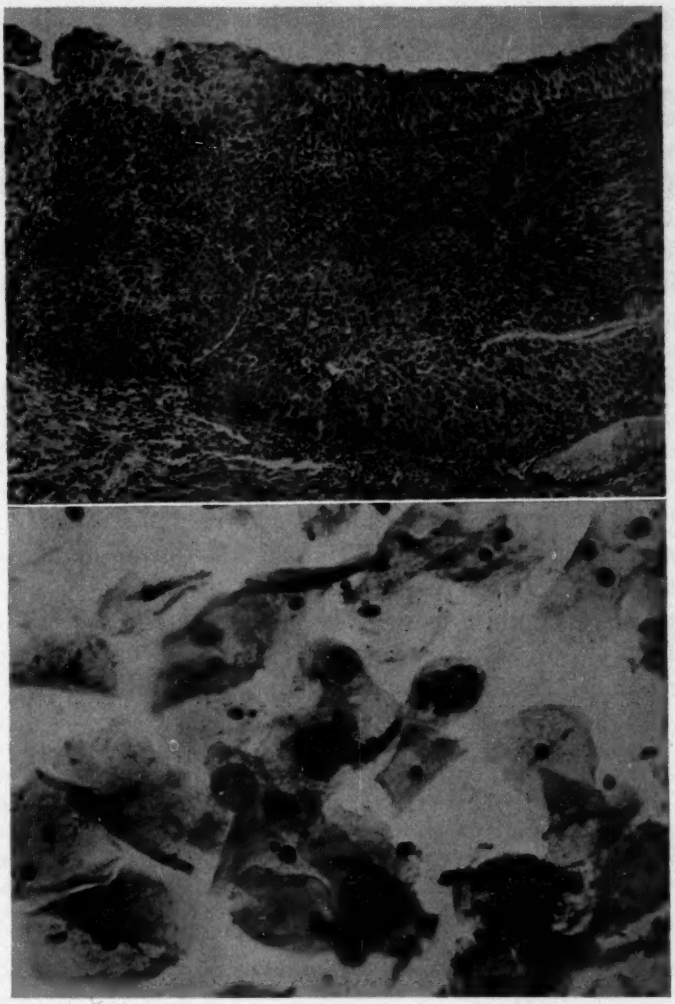

Fig. 6.

Fig. 5 (Case 51).—Carcinoma in situ with gland involvement and possible early stromal invasion. Epithelium shows loss of cell differentiation and polarity, hyperchromatism, and numerous mitoses. Tumor cells have almost filled gland lumen.

Fig. 6.—Same case as Fig. 5. Vaginal smear with a clump of poorly differentiated malignant cells. Note resemblance to those in tissue specimen.

Summary

1. The initial vaginal smears obtained in 60 cases of carcinoma in situ were correctly diagnosed on first examination in 70 per cent.

2. The highest diagnostic accuracy attainable by the vaginal smear technique in cases of carcinoma in situ of the cervix was found to be 82 per cent.

3. Vaginal smears were accurate in 54 per cent of 24 cases showing only surface malignancy, and were correct in 81 per cent of 36 cases with glandular involvement.

4. The average age found in this series was 35.2 years, 25 per cent of the patients being under 30 years of age. Twenty patients complained of abnormal bleeding on admission, and 40 had leucorrhea or were asymptomatic; only 9 per cent of the patients were found to have cervices that bled easily on examination.

5. A positive smear should be regarded with extreme caution and every effort made to confirm the diagnosis and locate the lesion before the patient is treated. A positive smear should *never* be considered as providing conclusive evidence of the disease.

6. Cervical aspirations contain more numerous cervical cells, and when submitted with a vaginal smear in a suspicious case will often facilitate a diagnosis of malignancy.

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245 Pond Avenue.

THE CEREBRAL EFFECTS OF PAPAVERINE HYDROCHLORIDE IN TOXEMIA OF PREGNANCY

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ALTHOUGH toxemia of pregnancy still remains as one of the great enigmas in medicine, the development by Kety and Schmidt[1] of a quantitative method of determining cerebral blood flow has allowed, for the first time, a significant study of the altered physiology of the brain in this disease.

It will be recalled that this method[2, 3] involves simultaneous withdrawal of venous blood from the jugular bulb and arterial blood from the femoral artery over a period of 10 minutes while the patient is breathing a mixture of 15 per cent nitrous oxide in air. Mean arterial blood pressure is measured directly from the femoral artery during the experiment. Cerebral blood flow (CBF) is measured in cubic centimeters per 100 Gm. of brain per minute. The cerebral metabolic rate in terms of oxygen (CMR_{o_2}) in cubic centimeters of oxygen utilized per minute by each 100 Gm. of brain, and the cerebral vascular resistance (CVR) in millimeters of mercury pressure per cubic centimeter of blood per 100 Gm. of brain per minute were calculated as previously described.[1]

The mean values of mean arterial blood pressure, cerebral blood flow, cerebral vascular resistance, and cerebral metabolic rate in terms of oxygen upon 15 normal women between 34 and 40 weeks' gestation, 23 patients with pre-eclamptic toxemia, and 21 patients with hypertensive toxemia are shown in Table I. These values are approximately the same as those reported in our earlier work.[4, 5]

TABLE I. MEAN VALUES OF CEREBRAL BLOOD FLOW AND METABOLISM

	NORMAL (15 CASES)	PRE-ECLAMPSIA (23 CASES)	HYPERTENSIVE TOXEMIA (21 CASES)
MABP	86	118#	124*
CBF	56	54	54
CMR_{o_2}	3.7	3.7	3.3
CVR	1.5	2.5#	2.3*

*Differs significantly from normal when using the "t Test" ($p < 0.05$).

It is noted that aside from the expected elevation in mean arterial blood pressure, there is no significant difference between normal pregnant women and those with pre-eclamptic and hypertensive toxemia except in the cerebral vascular resistance. This is looked upon as being most likely due to angiospasm.

Because of this assumption it was decided that a study of the effect of vasodilating drugs upon this increased cerebral vascular resistance in toxemic pregnant women would be of interest. Several such drugs are to be used and compared in the larger study. This paper is a report of the effect of papaverine hydrochloride in such patients.

Papaverine hydrochloride, an opium derivative causing relaxation of smooth muscle by direct action, was chosen not only because of its vasodilating effect and comparative lack of toxicity, but also because the experiments of others suggest that it has an especially definite effect upon the vessels of the brain. In 1926 Gruber and Roberts[6] surmised that papaverine had this action and since that time others[7] have reached this conclusion. In 1935 Bouckaert and Jourdan[8] using isolated brain preparations with a constant perfusion rate in dogs demonstrated definite evidence of dilatation of the cerebral vessels with this drug. Recently Russek and Zohman[9] used papaverine in neurological patients suffering from cerebral episodes thought to be due to angiospasm. Some of these were hypertensive. The marked clinical success which these authors had with papaverine in such cases made them suggest its use in other conditions, supposedly characterized by cerebral vasospasm, including eclampsia gravidarum. In a review of the literature since 1900, no instance of the use of papaverine hydrochloride for the treatment of the toxemias of pregnancy was found.

Method

In this study determinations of cerebral blood flow and metabolism were made both before and after the administration of papaverine in each case. The dose varied from 1 to 3 grains, the usual dose being 2 grains intravenously or 3 grains intramuscularly. The drug occasionally produced a sensation of dizziness for a few minutes, but no other untoward effects were noted. A mild hypnotic effect was usually evident for a period of one to two hours. The second determinations were done 30 to 60 minutes after administration of the drug.

Material

Seven patients with pre-eclampsia and three patients with hypertensive toxemia were treated with papaverine. The pretreatment values in these patients did not differ significantly from the values previously established[5] for pre-eclampsia and hypertensive toxemia so that they may be looked upon as representative cases.

TABLE II. MEAN ARTERIAL BLOOD PRESSURE BEFORE AND AFTER TREATMENT WITH PAPAVERINE (NORMAL 86 MM. HG)

	BEFORE TREATMENT	AFTER TREATMENT	PER CENT CHANGE
Pre-eclampsia.—			
Case 1	152	100	−34
2	101	78	−23
3	141	126	−11
4	120	114	− 5
5	109	96	−12
6	116	91	−22
7	107	62	−42
Hypertensive toxemia.—			
Case 1	139	103	−26
2	94	94	0
3	111	95	−14

After treatment with papaverine, the mean arterial blood pressure declined an average of 21 per cent in the pre-eclamptic group and 13 per cent in

the hypertensive group. The only patient not showing a fall in blood pressure demonstrated a relatively low value (94 mm. Hg) before treatment was given.

TABLE III. CEREBRAL BLOOD FLOW BEFORE AND AFTER TREATMENT WITH PAPAVERINE

(Normal 58 c.c./100 Gm. brain/min.)

		BEFORE TREATMENT	AFTER TREATMENT	PER CENT CHANGE
Pre-eclampsia.—				
Case	1	53	45	−15
	2	68	72	+ 6
	3	69	75	+ 9
	4	67	80	+19
	5	56	79	+41
	6	47	67	+43
	7	39	51	+31
Hypertensive toxemia.—				
Case	1	75	86	+15
	2	47	86	+83
	3	41	45	+10

Papaverine brought about an average increase in cerebral blood flow of 19 per cent in the pre-eclamptic group and 36 per cent in the hypertensive group. This is a significant increase over the mean pretreatment values.

TABLE IV. CEREBRAL VASCULAR RESISTANCE BEFORE AND AFTER TREATMENT WITH PAPAVERINE

(Normal 1.5 mm. Hg/c.c./100 Gm. brain/min.)

		BEFORE TREATMENT	AFTER TREATMENT	PER CENT CHANGE
Pre-eclampsia.—				
Case	1	2.8	2.2	−21
	2	1.5	1.0	−33
	3	2.4	1.7	−29
	4	1.8	1.4	−22
	5	1.9	1.2	−37
	6	2.4	1.3	−46
	7	2.5	1.2	−52
Hypertensive toxemia.—				
Case	1	1.8	1.2	−33
	2	2.0	1.0	−50
	3	2.7	2.1	−22

TABLE V. CEREBRAL METABOLIC RATE IN TERMS OF OXYGEN BEFORE AND AFTER TREATMENT WITH PAPAVERINE

(Normal 3.7 c.c. O_2/100 Gm. brain/min.)

		BEFORE TREATMENT	AFTER TREATMENT	PER CENT CHANGE
Pre-eclampsia.—				
Case	1	3.4	4.0	+18
	2	4.2	4.1	− 2
	3	4.6	4.7	+ 2
	4	4.4	5.1	+16
	5	4.2	5.5	+31
	6	4.1	5.9	+44
Hypertensive toxemia.—				
Case	1	3.3	5.2	+58
	2	2.7	5.4	+100
	3	2.4	2.6	+8

With papaverine the cerebral vascular resistance was significantly reduced to the normal range in almost every case. The average decrease in pre-eclampsia was 34 per cent and in hypertensive toxemia 35 per cent.

The oxygen utilization by the brain was increased by papaverine in all but one instance. There was a significant average elevation of 18 per cent in the pre-eclamptic group and 55 per cent in the smaller group with hypertensive toxemia.

TABLE VI. CHANGES IN CEREBRAL BLOOD FLOW AND METABOLISM AFTER ADMINISTRATION OF PAPAVERINE

(10 Cases of Pre-eclampsia and Hypertensive Toxemia)

	MEAN BEFORE TREATMENT	MEAN AFTER TREATMENT	DIFFERENCE BETWEEN MEAN	MEAN PERCENTAGE CHANGE
MABP	119.0	95.9	−23.1†	−19
CBF	56.2	68.6	+12.4‡	+24
CVR	2.18	1.43	−0.75†	−35
CMR_{o2}	3.70	4.72*	+1.02‡	+31

*Only 9 of the 10 patients had CMR_{o2} calculated.

† and ‡Signifies statistically significant differences from control observations. (†$p < 0.01$; ‡$p < 0.02$).

Because the cerebral changes are approximately the same in pre-eclampsia and hypertension with superimposed toxemia, the ten cases studied have been combined in Table VI.

Comment

This study offers evidence that papaverine hydrochloride has a marked effect, not only by lowering the blood pressure, but also by the favorable alteration of certain aspects of cerebral physiology, in patients suffering from the nonconvulsive toxemias of pregnancy.

There is a remarkable lowering of the typically elevated cerebral vascular resistance in these cases to the normal range. In a previous communication[5] it was pointed out that the increased cerebral vascular resistance in toxemia might be due to an intrinsic action within the vessels themselves such as vasospasm, to an extrinsic pressure caused by edema or increased viscosity or sludging of the blood. As pointed out earlier in this presentation, the study of vasodilating drugs was started because of the assumption that the overwhelming factor in the increased cerebral vascular resistance in toxemias of pregnancy is vasospasm. This thesis is well supported by the pronounced effect of papaverine in decreasing this resistance in so rapid a manner. The other factors mentioned could hardly be affected so quickly.

The increase in cerebral blood flow is probably brought about by the fact that the cerebral vascular resistance is lowered to a greater degree than the mean arterial blood pressure. This would seem to be due to the more pronounced vasodilating effect of papaverine upon the vessels of the brain.

Last, there is a significant elevation of oxygen utilization by the brain. This is looked upon as a most favorable effect inasmuch as a definite depression of this function has been shown to be present in eclampsia with convulsions,[5] and unpublished work by the authors reveals that sedatives routinely used in this disease have a similar influence.

It would appear that the relief of cerebral vasoconstriction with the resultant increase in cerebral blood flow and oxygen utilization by the brain should be most desirable in the therapy of toxemia of pregnancy. It is therefore suggested that papaverine hydrochloride be given a thorough clinical trial as at least an adjunct to other therapy in this disease. One of the drawbacks is its transient effect when given in intermittent dosage. Recently continuous intravenous infusions of the drug have been used in severe pre-eclampsia with encouraging results.

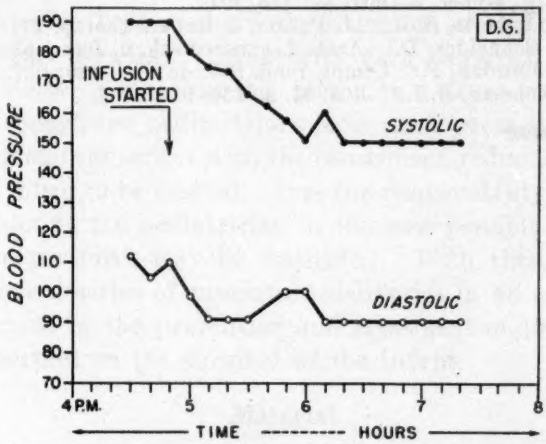

Fig. I PAPAVERINE HCl INFUSION.
6 Grains in 500 cc. of distilled water with 20% glucose.

Figure 1 shows the decrease in blood pressure brought about by the administration of 6 grains of papaverine in a solution of glucose and water over a period of three hours in a typical case of severe pre-eclampsia.

Summary

1. With the use of the nitrous oxide method of Kety and Schmidt, the cerebral blood flow and related circulatory and metabolic functions of the brain were studied both before and after the administration of papaverine hydrochloride to a group of women with pre-eclampsia and hypertensive toxemia of pregnancy.

2. No untoward effects were caused by this drug.

3. Papaverine hydrochloride brought about the following changes in the nonconvulsive toxemias of pregnancy:

a. Significant lowering of mean arterial blood pressure.

b. Significant and rapid decrease of cerebral vascular resistance to normal.

c. Significant increase of cerebral blood flow.

d. Significant increase in the oxygen utilization by the brain.

4. The possible value of this drug in toxemia of pregnancy is discussed and it is concluded that it should be given a thorough clinical trial as an adjunct to the therapy of this disease.

This study was supported by the Obstetrical and Gynecological Fund of the Jefferson Hospital. The authors wish to acknowledge the active interest shown in this work by Drs. Thaddeus L. Montgomery and Lewis C. Scheffey of the Jefferson Medical College. Appreciation is also due to Phyllis Potash, technician, and Barbara Sigmond, statistician.

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AN ANALYSIS OF PREMATURE DELIVERY OF LIVEBORN INFANTS

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GREAT progress has been made in the reduction of the neonatal death rate in the past two decades. Prematurity as a cause of neonatal mortality still ranks high, Potter estimating this factor as a cause in more than 50 per cent of cases. Although the pediatricians have made great strides in knowledge and care of the premature infant with the consequent reduction in the mortality rate, there is still much to be desired. It is the responsibility of the obstetrician to present an infant to the pediatrician in the best possible condition in order that new effective measures may be instituted. With these facts in mind, it is feasible to review a series of premature deliveries in an effort to learn what factors are important in the prevention and treatment of premature labor and those factors important in the survival of the infant.

Material

The study to be presented is one of 582 consecutive cases of premature liveborn infants delivered from Sept. 1, 1943, through Dec. 31, 1949, at the Norwegian Hospital, Brooklyn, N. Y. The former date represents the opening of a separate building for maternity patients with the establishment of a special nursery for the care of prematures. During the time period named, there was a total of 8,836 deliveries at this institution, the deliveries of premature liveborn infants representing 6.58 per cent of this total. As defined by the American Society of Pediatrics, any infant under 2,500 grams, regardless of body length, was considered as premature. Only those patients with a duration of pregnancy longer than 26 weeks were admitted to the maternity division and therefore subsequently included in this study. As recommended by Henderson, only liveborn infants were considered even though some had congenital anomalies incompatible with life.

Some of the general characteristic factors of this group of patients should now be mentioned. The average age of the parturient woman in this series was 28.0 years, which is practically the same as the average for all maternity patients at this institution. Calculated according to the dates given by the patient, the average gestation was 36.1 weeks in duration. The annual incidence of premature labor in this series did not vary significantly over the years studied when these figures were tabulated.

The patients under consideration were all registered in this institution and all had adequate prenatal care. No Negroes are included in this study. Four hundred eighty cases were private, and 102 patients were general service patients from the prenatal clinic. The ratio of private to service patients compares favorably with the ratio of all patients in the maternity division.

Eastman has postulated that the majority of premature labors may be due to a dietary deficiency. In our institution, much stress is placed upon adequate diets and supplementary vitamins both in the clinic and as regards the care of

private patients. A possible idea of the adequate diet ingested during pregnancy in this series is the average weight gain of 19.9 pounds which seems to indicate a probable adequate intake. Yet the incidence of delivery of premature liveborn infants was 6.58 per cent, which does not compare favorably with those of other series (Eastman 11.7 per cent, Tyson 9.4 per cent, Dana 2.95 per cent, these figures including both stillborn and liveborn premature infants). Hence no indication that dietary deficiency can be a factor in premature delivery is found in this series.

Etiological Factors in Premature Delivery

Delivery in primiparas occurred in 287 cases, and in multiparas in 295 cases. Primigravidas delivered 228 infants, and 72 patients had a history of previous spontaneous abortions. These figures do not differ much from the proportion in mothers admitted to this institution. Significant, however, was the history of having had previous premature infants. In 52 instances this was the case and represented about three times the incidence of the general maternity admissions. This tendency for certain patients to have premature infants has been noted by other observers. Possibly it represents an inability of the uteri of these women to accommodate the normal-sized fetal ovoid at term because of the underdevelopment of the uterine muscle. A probable corollary of this thought is that in 187 instances, or 31 per cent, spontaneous rupture of the

TABLE I. MATERNAL COMPLICATIONS IN PREMATURE DELIVERY

		NUMBER	INCIDENCE (PER CENT)
No complications found		296	50.8
Toxemias of pregnancy		78	13.4
Pre-eclampsia, mild	41		
Pre-eclampsia, severe	23		
Nephritis, chronic	2		
Nephritis, acute	1		
Essential hypertension	10		
Eclampsia	1		
Multiple pregnancy		72	12.3
Premature separation of placenta		27	4.6
Previous uterine surgery		20	3.4
Myomectomy	1		
Fothergill operation	3		
Previous section	14		
Uterine suspension	2		
Placenta previa		19	3.2
Partial	10		
Complete	4		
Marginalis	5		
Cardiac disease		14	2.4
Rheumatic heart disease, inactive	12		
Congenital heart disease	1		
Subacute bacterial endocarditis	1		
Pyelitis, acute		5	0.8
Fibromyomata uteri		3	0.5
Intrapartum infection		1	0.2
Pulmonary tuberculosis, inactive		2	0.4
Tuberculosis, hip		1	0.2
Diabetes mellitus		1	0.2
Hyperthyroidism		2	0.4
Syphilis, treated		2	0.4
Pernicious anemia		1	0.2
Rising Rh antibody titer		3	0.5
Grand multipara		1	0.2
Elderly primipara		28	4.7
Hydramnios		6	1.0

membranes occurred prior to labor. In normal labor, this occurs in about 20 to 25 per cent of cases.

Table I shows the complications in this group in their order of frequency. In the majority of patients, no complications were evident, which is in agreement with other series of premature deliveries where no definite etiology can be ascribed.

The most common complication recorded was that of the toxemias of pregnancy. This factor in premature delivery occurred in 78 cases, or 13.4 per cent of the total, a figure which is almost three times the incidence in all maternity patients. Obviously toxemia of pregnancy plays an important part in premature delivery but other associated conditions must be noted as contributing factors. These include premature separation of the placenta, multiple pregnancy, and elective termination of pregnancy by induction of labor or cesarean section for those cases of sever pre-eclampsia.

Multiple pregnancy, all twins except one case of triplets, was present in 72 cases, or 12.3 per cent, and represented the second most important complication in this series. Here again one may postulate that the etiological factor is an overdistention of the uterus with inability of the uterine muscle to accommodate the fetal contents.

In 27 instances, or 4.6 per cent, premature separation of the placenta was noted as a complication. At this institution, all cases which show evidence of placental separation are included in this category even though no classic signs or symptoms are present and the diagnosis is made at delivery where adherent clots are noted at the edge of the placenta. Possibly this accounts for our higher average than that noted in other series. In only 4 patients was an associated pre-eclampsia evident with this complication. In the remainder of instances, no definite cause for placental separation could be found.

The next most frequent complication present as a possible etiological factor in premature labor was that in which previous surgery of the uterus was a factor. Previous cesarean section was the surgery in the majority of these cases. In most of these patients, the onset of premature labor was treminated by repeat cesarean section according to the practice in this hospital. The total of patients with previous uterine surgery was 20, or 3.4 per cent.

Placenta previa of all types was an etiological factor in 19 cases, or 3.2 per cent. In about three-fourths of these patients, labor was induced or pregnancy terminated by cesarean section because of this condition. It is evident that in cases of placenta previa the obstetrician necessarily terminates the pregnancy as a lifesaving measure for both the mother and the fetus.

As noted in Table I, other complications such as heart disease, pyelitis, fibromyomata uteri, diabetes mellitus, hyperthyroidism, treated syphilis, and pernicious anemia could not be ascribed as etiological factors in premature delivery. However, in one case a severe intrapartum infection of unknown etiology definitely caused premature labor. Three pregnancies were terminated prior to term because of a rising Rh antibody titer, one patient being delivered by cesarean section.

Intrapartum Factors

In our series, the average length of labor in the primiparous patient was 8.5 hours and in the multipara 5.1 hours. These figures are much less than the usually quoted averages of 18 hours for primiparas and 12 hours for multiparas seen in all parturient women.

Table II shows the incidence of the various presentations in this series of premature delivery. It is notable that the frequency of abnormal presentations

is high, the frequency of breech and face presentation being increased about four times that seen at term. This is in accord with other observations of premature delivery and may be a factor in the neonatal mortality.

TABLE II. PRESENTATION IN PREMATURE DELIVERY

	NUMBER	INCIDENCE (PER CENT)
Vertex	474	81.5
Breech	102	17.5
Face	4	0.8
Transverse	1	0.1
Unknown	1	0.1
Total	582	100.0

Some interesting observations are noted upon reviewing the series with the idea of sedation during labor in mind. Three hundred thirty-six infants, or 57.7 per cent, were delivered with no analgesic given during labor. Eleven mothers, or 1.9 per cent, were under the influence of morphine analgesia during labor with 3 neonatal deaths resulting, or about 25 per cent fatalities in this group of 11 cases. This is in agreement with the well-known observation that morphine has a marked depressant and injurious effect on the infant. It might be mentioned that in most of the cases in which morphine was given it was used in an attempt to prevent the onset of premature labor. In 40.4 per cent of the deliveries, or 235 cases, Demerol analgesia in the dosage of 100 mg. was used during labor with only 9 deaths in this group. A review of the cases of neonatal death in which the mothers had received Demerol analgesia during labor shows that only 2 infant deaths could possibly be attributed to this drug. Lull and Hingsom state that prematures are definitely not narcotized to a degree comparable to that often seen with morphine. This series attests to the apparent harmlessness of Demerol analgesia in the conduct of premature labor.

TABLE III. METHOD OF DELIVERY

	NUMBER	INCIDENCE (PER CENT)
Spontaneous vertex	338	58.1
Low forceps	94	16.1
Cesarean section	50	8.6
Assisted breech	44	7.5
Spontaneous breech	32	5.5
Breech extraction	16	2.7
Spontaneous face	4	0.8
Version and breech extraction	3	0.5
Midforceps	1	0.2
Total	582	100.0

Light inhalation anesthesia for the actual delivery was given in 387 cases, or 66.4 per cent. Most authorities do not advise using a general anesthetic in premature delivery, but no harmful effects could be definitely proved in this series. Possibly this is due to the light anesthesia given here, which is administered for only a short time prior to delivery, so that anesthetic levels in the fetus were small. Emphasis was placed on adequate oxygenation during this type of anesthesia. In 149 cases, or 25.6 per cent, spinal and local anesthesia was administered. These included most of the deliveries by cesarean section. This type of anesthesia is to be encouraged in premature delivery but sometimes the precipitous type of delivery does not allow ample time for it. This accounts for the low percentage of this type of anesthesia. Finally, in 8 per cent of patients, or 46 cases, no anesthesia was given.

Table III gives the incidence of the various forms of delivery in our series. The majority of deliveries, 58.1 per cent, were spontaneous vertex, while the

incidence of low forceps was 16.1 per cent, which is slightly less than the proportion in all maternity patients in this institution. The use of low forceps for delivery of premature infants is favored by many men at this hospital; however, others favor spontaneous delivery and in many cases the short second stage of premature labor precludes the use of forceps. The high proportion of breech extraction and assisted breech deliveries is traced to the high number of breech presentations in this series. By assisted breech, we denote assistance to the arms and the aftercoming head whether this be by forceps or manually. Cesarean section was employed in 8.6 per cent of the total cases which is about twice the rate of all patients in the maternity division. In this series section was used in most cases of placenta previa, fulminating toxemia, and premature separation of the placenta which necessarily forced the obstetrician to act. Episiotomy was performed in 344 cases, or 59.1 per cent, which is somewhat more than the average incidence.

Infant Mortality

In a review of the infant deaths in this group, no significant change in the annual incidence during the years studied was apparent. A total of 65 deaths during the neonatal period, or 11.2 per cent of the 582 cases, was the over-all mortality. If the infants and deaths in those infants under 1,000 grams are excluded, as is done in statistics on prematurity, we arrive at a total of 557 cases with 43 infant deaths, or a mortality rate of 7.7 per cent. Further, if, in this corrected group, we exclude those deaths due to congenital anomalies incompatible with life, we exclude 4 deaths, leaving 39 deaths, or a mortality rate of 7 per cent.

TABLE IV. MORTALITY RATE ACCORDING TO WEIGHT OF INFANT

WEIGHT IN GRAMS	NUMBER	DEATHS	INCIDENCE (PER CENT)
Below 1,000 grams	25	22	88.0
1,000-1,249	18	6	33.3
1,250-1,499	28	11	39.3
1,500-1,749	52	7	13.5
1,750-1,999	64	5 (4)	7.8 (6.2)
2,000-2,249	134	11 (8)	8.2 (5.9)
2,250-2,499	261	3	1.2

Table IV represents a breakdown of the neonatal deaths according to the birth weight. We note an 88 per cent death rate in those infants below 1,000 grams. The remaining infants are classified in 250 gram weight groups. With the exception of the 1,250 to 1,499 gram group, we note a gradual decrease in the neonatal death rate as the weight of the infant increases. This factor of birth weight is most important in the survival of the premature infant. The only correction in the number of deaths and the mortality rate for congenital anomalies occurs in the fifth and sixth groups and appears in parentheses beside the uncorrected figures.

Before presenting an analysis of the conduct of labor and delivery in the cases of these infant deaths, it might be feasible briefly to describe the conduct of premature labor and delivery at this institution. When a patient is admitted with premature rupture of the membranes, no measures are used to stimulate the uterus in an effort to delay labor. When in labor, the mother is given oxygen, and analgesic drugs which cause anoxia in the fetus are avoided. Vitamin K is administered to all these women in labor.

For delivery, a generous episiotomy is made even though the infant is small. Fundal pressure is avoided, some of the attending physicians using low forceps

not for traction but as protection for the cranium. The infant is delivered into a warm sterile blanket, the nasopharynx lightly aspirated of mucus, and oxygen given by face mask. A minimum of handling is emphasized and the infant is taken to the premature nursery immediately in an incubator.

TABLE V. FACTORS IN INFANT MORTALITY

	NUMBER OF CASES	DEATHS	INCIDENCE (%)
Type of Delivery.—			
Spontaneous vertex	325	19	5.8
Low forceps	84	5	5.9
Spontaneous breech	28	7	25.0
Assisted breech	44	1	2.3
Cesarean section	50	6	12.0
Spontaneous face	4	1	25.0
Episiotomy	344	24	6.9
Analgesia.—			
Morphine	11	3	27.2
Demerol	225	9	4.0
None	317	27	8.5
Anesthesia.—			
None	46	6	13.0
General	368	18	4.9
Regional	139	15	10.7
Complications.—			
Premature separation of placenta	27	6	22.2
Pre-eclampsia, mild	41	1	2.4
Pre-eclampsia, severe	23	3	13.0
Multiple pregnancy	72	5	6.9
Placenta previa	19	3	15.7
Pernicious anemia	1	1	100.0
Intrapartum infection	1	1	100.0

The analysis to be presented includes only those infants above 1,000 grams. A glance at the composite Table V shows the various factors important in the mortality of premature infants of this group. Here are compiled the various types of delivery, analgesia, anesthesia, and complications of labor with the number of cases in each group and the resultant mortality. By a study of these figures, we may learn what possibly should be avoided to prevent premature neonatal deaths. The mortality incidence as regards method of delivery shows no difference in those infants delivered from vertex presentation by either low forceps or spontaneous delivery (5.9 per cent and 5.8 per cent, respectively). Significantly high was the mortality rate (25 per cent) when the presentation was a breech even though the delivery was spontaneous. The inherent dangers of breech presentation are increased in prematurity and intracranial injury is more evident, due to the weakness of the premature's tissues. A 12 per cent mortality rate was recorded for those infants delivered by cesarean section which is almost twice the total mortality rate of this series. However cesarean section was done primarily in those cases in which a certain amount of fetal distress was already present, placenta previa, premature separation of the placenta, and fulminating pre-eclampsia.

A study of the infant deaths as regards the analgesia used during labor has already been commented upon. The figures of the types of anesthesia and infant mortality show no significant features. General anesthesia gave a mortality rate of only 4.9 per cent while the figures for no anesthesia (13.0 per cent) and for regional anesthesia (10.7 per cent) are somewhat higher than the composite mortality rate. The latter figure is probably high due to the complicated cases in which delivery was by section and the use of spinal anesthesia in them. From this study, no definite conclusion condemning or sanctioning one type or another of anesthesia can be made.

The maternal complications in this group of infant deaths show a higher infant mortality rate than the general rate in those cases of premature separation of the placenta (22.2 per cent), placenta previa (15.7 per cent), and severe pre-eclampsia (13.0 per cent). In these instances the fetus was probably subjected to a high degree of asphyxia prior to delivery which would account for the high mortality rates. A conclusion from the figures in this portion of the table leads us to believe that maternal complications that cause fetal anoxia and cause the obstetrician to terminate the pregnancy prematurely are paramount factors in a high fetal mortality.

There was no relationship between the duration of labor and infant mortality in this study. The sex of the infant was no factor in mortality, as 19 female infants and 20 male infants died.

TABLE VI. CAUSES OF DEATH IN PREMATURE INFANTS

	NUMBER	INCIDENCE (PER CENT)
Prematurity alone	19	44.2
Intracranial hemorrhage	10	23.2
Pulmonary atelectasis	8	18.6
Erythroblastosis fetalis	2	4.6
Congenital anomalies	4	9.4

Table VI shows the various causes of infant mortality recorded in this series. Autopsies were performed on 19 infants or about one-half the group. The causes of death were discovered at autopsy or, in those cases where autopsy was refused, the pediatrician ascribed the cause of death according to his clinical judgment. Prematurity alone comprised 44.2 per cent of the causes, while intracranial hemorrhage ranked next with 23.2 per cent. Pulmonary atelectasis accounted for 18.6 per cent of deaths while erythroblastosis fetalis was the factor in 4.6 per cent. Congenital anomalies accounted for 9.4 per cent of deaths. It seems that in the majority of cases the premature's tissues are not ready for life, and death can be ascribed only to prematurity. Underdeveloped tissues in the cranium and lungs cause the high incidence of intracranial hemorrhage and pulmonary atelectasis.

Summary and Conclusions

1. A series of 582 premature liveborn infants born to patients all registered and all having had adequate prenatal care has been presented. The incidence of premature deliveries was 6.58 per cent.

2. The majority of cases presented no evident etiology. Toxemias of pregnancy, multiple pregnancy, premature separation of the placenta, placenta previa, and previous uterine surgery were major complications causing premature delivery. If any improvement in neonatal mortality in prematures is to be sought, the obstetrician should direct his attention to preventing these conditions if possible, and where the condition already exists, his aim should be to obtain a larger, more viable fetus to present to the pediatrician upon birth.

3. A spontaneous or low forceps delivery was found to be best for the premature infant. Demerol analgesia was not found to be harmful during labor in contradistinction to morphine. In this study, the anesthesia seemed to make little difference in the results.

4. The corrected infant mortality was recorded as 7.0 per cent, the larger infant having the better chance of survival. A high mortality rate was present

in breech presentations. Any condition causing fetal anoxia, and particularily premature separation of placenta, placenta previa, and severe pre-eclampsia in the mother accounted for a high fetal mortality.

5. The majority of infant deaths were traced to the inability of the premature's vital organs to stand the rigors of delivery and vital functions after birth. Prematurity alone and intracranial hemorrhage were the principal causes of death.

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MORBIDITY AFTER TOTAL ABDOMINAL HYSTERECTOMY

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AFTER a discussion of morbidity for the average gynecologic operation and because tables were not available that seemed to control the many variables that arise in studies of surgical patients, a program was set up to evaluate some of the factors affecting postoperative morbidity. Total abdominal hysterectomy was chosen, since it is one of the most commonly employed gynecologic techniques and is done sufficiently frequently to facilitate statistical analysis of the different steps. Our study of three series of cases was undertaken to determine the effect on surgical morbidity of (1) preoperative vaginal preparation on the operating table, (2) intraperitoneal sulfathiazole, and (3) simultaneous appendectomy of patients undergoing total abdominal hysterectomy.

A universally accepted standard of surgical morbidity has not been established; hence, the criteria for morbidity in the literature vary widely. The standard most frequently used, obtained from the obstetric morbidity standard, defined morbidity as a temperature (oral) of 100.4° F. or higher on any two postoperative days, excluding the day of operation.

This standard was used by Smith,[11] who reported a morbidity rate of 46.0 per cent in 93 cases of total abdominal hysterectomy and by Danforth[2] with a morbidity rate of 28.2 per cent in 500 cases. By the same criteria, Jones and Doyle[3] reported a morbidity rate of 36.57 per cent in 380 cases and emphasized the fact that difficult technical procedures and residues of pelvic infection increase morbidity. They also distinguished between "physiologic" and "pathologic" morbidity, and offered composite temperature curves as guides. In 40.2 per cent of their cases in which a state of morbidity existed the cause was not found.

In a study of 1,925 cases, Mengert and Stoltz[4] used 100.4° F. as the division between normal and febrile postoperative courses and found that 11 per cent of the patients were afebrile and that 16 per cent had fever for one day, 73 per cent for two or more days, and 55 per cent for not more than three days. The average peak temperature in these cases was 101.3° F. Mohler and Bishop[6] reported a febrile reaction, of unstated degree, which lasted for seventy-two hours immediately after operation in 21 of their 100 cases. In addition to those patients with known complications, Phillips[9] found 19.8 per cent of 643 patients to have an unexplained elevation of temperature (degree not stated) and pulse rate during the first two to four days after operation.

Tyrone and associates[12] defined morbidity as a temperature of 100.4° F. for two consecutive days and reported a rate of 22.4 per cent in 478 cases. Peterson[7] used the same temperature of 100.4° F. or more for a period of any

two consecutive days, including the day of operation, as his criterion for a morbid state and reported a morbidity rate of 13.63 per cent in 110 cases of total abdominal hysterectomy. In 81 per cent of his cases 60,000 to 100,000 Oxford units of penicillin were given every three hours until a total of forty doses was reached. Reich and Nechtow[10] also advocated giving penicillin for three or four days routinely postoperatively; morbidity figures were not given. Miller and Prejean[5] found 20.9 per cent of 374 patients to have a temperature of 100.4° F. on three successive days, excluding the first twenty-four hours. These authors defined normal hospital stay as fourteen days after total abdominal hysterectomy.

In 1,273 cases of panhysterectomy, Weir[13] found that 59.9 per cent of the patients had temperatures of less than 101.3° F., 20.2 per cent had temperatures of more than 101.3° F. for one day, and 19.9 per cent had temperatures of more than 101.3° F. for more than one day. Preparation of the vagina in the operating room, although not mentioned in the majority of reports already cited, was however, an integral part of the technique employed by Mengert and Stoltz,[4] Mohler and Bishop,[6] and Reich and Nechtow[10] in an attempt to decrease morbidity. They reported that when the patient was brought to the operating room, the vagina was scrubbed with soap and water, after which an antiseptic agent was used intravaginally.

Rather than attempt to cleanse or sterilize the vagina, Cianfrani and Zeigerman[1] isolated the vagina at operation by elevating the vaginal wall and inserting a sponge from above. Their figures regarding morbidity are not amenable to comparison; 101 of 130 patients had normal temperatures within one week and were free of complications.

Little mention is made in the literature regarding the intraperitoneal use of sulfonamide drugs in total abdominal hysterectomy. None of the foregoing reports contained comments on their use. Phaneuf[8] stated that in the early days of sulfonamide drugs, he placed sulfanilamide or sulfathiazole in the pelvis. He further stated that "in a comparable series, with or without these remedial agents, it has been proved to my satisfaction that there is but little or no difference in the postoperative period." He did not make any statement as to preparation of the vagina and did not give figures relative to morbidity. At the time of our report a further factor is playing its part in the routine use of sulfonamides at operation. So many patients have received sulfonamides previously that the incidence of reactions to the drugs appears to be increasing and in time the risk and discomfort of allergic reactions may well make the routine use of the drugs objectionable.

Simultaneous appendectomy was not performed routinely by Jones and Doyle[3] in cases of total abdominal hysterectomy. Danforth[2] similarly stated that a conservative attitude toward appendectomy is wise and omitted it if the hysterectomy was difficult. Weir,[13] Smith,[11] Phillips,[9] and Cianfrani and Zeigerman[1] reported that simultaneous appendectomy did not increase the morbidity rate in their cases and advocated removing the appendix whenever possible.

Materials and Methods

Three series of cases, one for each of the three years, 1947, 1948, and 1949, formed the basis of our study. Each series was composed of cases in which the patient had undergone total abdominal hysterectomy. The preoperative preparation and the postoperative care of all patients were under the direction of one surgeon (Pratt) who also performed all of the operations. The patients studied were operated on in one of two hospitals in 1947, and in only one hospital in 1948 and 1949. Only the patients operated on in the first three quarters of

each year were included as this gave us more than 100 patients for each series. The technique of the operation was the same during the three years, but a gradual change occurred in that in the later years Pentothal Sodium and curare were administered intravenously more frequently in place of nitrous oxide-oxygen-ether anesthesia. The only other change was earlier ambulation of the patients. In 1947, patients remained in bed four to five days while in 1949 practically all patients were out of bed at the end of two days. Early ambulation with its resulting feeling of strength and well-being at the end of seven to eight days, in our opinion, has been the principal factor in reducing the hospital stay from twelve to 10.6 days per patient and has perhaps been a factor in the reduction of the postoperative morbidity.

The first postoperative day is considered to last until midnight of the day of operation regardless of the time of day the operation was performed. Succeeding postoperative days are counted from midnight to midnight. Morbidity rates were determined on the basis of elevation of oral temperature to 100.4° F. or higher on any two days excluding the day of operation. On this basis we included as morbid patients whose temperatures were elevated at 11 p.m. of one day and 8 a.m. of the next day although all other determinations of temperature were below 100.4° F. and regardless of when the patient left the hospital.

Preoperative vaginal and perineal care of all patients was similar. The vulva and perineum were shaved the day before operation. A soapsuds enema was given the night before operation followed by a cleansing douche containing soda bicarbonate. The morning of operation a second cleansing douche was administered. In the series for 1947 after the patient had been anesthetized she was catheterized and the vagina was wiped out with two Merthiolate sponges. In 1948 and 1949 patients were placed in the lithotomy position after the anesthesia had taken effect. The vagina was scrubbed with sterile soap and water for five minutes, wiped out with Merthiolate and then the bladder was emptied. This five-minute scrub in the lithotomy position was the only difference in the vaginal toilet in the three series of patients.

Five grams of sulfathiazole crystals were used intraperitoneally for all patients included in the 1947 and 1948 series. In 1947, 4 patients did not receive sulfathiazole, 2 because of a history suggestive of sensitivity, 1 because of a leucocyte count of less than 4,000 per cubic millimeter of blood, and 1 for unknown reasons, and these were excluded. One of these 4 patients was considered to be morbid according to the standard we established for our study. In 1948, 2 patients did not receive sulfathiazole, 1 because of a history of sensitivity and 1 for unknown reasons. Neither patient had a morbid course and both of them were out of the hospital in less than fourteen days.

Seventeen other cases were also excluded from the 1947 series because the vagina was prepared in the operating room with soap and water as well as Merthiolate. Thirteen of these had preliminary dilatation and curettage before the abdominal operation and four others had vaginal repairs in addition to abdominal hysterectomy. Seven, or 41.1 per cent, of the 17 patients ran morbid courses. All but one, however, left the hospital on or before the fourteenth day, and that one left on the fifteenth postoperative day. It is also of interest that 9 of the 13 patients who underwent preliminary dilatation and curettage had malignant disease of the fundus.

No patients were excluded from the series for 1948 as all who had had vaginal repairs, dilatation and curettage had been prepared for operation in the routine manner. In 3 cases in which the small bowel was resected and in 1 case in which a cyst was removed from the lower pole of the kidney the usual amount of sulfathiazole had been administered.

Of the cases for 1949, 15 were excluded from our study because sulfathiazole was left in the abdomen. Only 1 of the 15 patients had a morbid postoperative

course and all but 1 left the hospital by the fourteenth day. The latter remained for seventeen days. Sulfathiazole was used because of large associated lipectomies, tuboovarian abscesses, questionable perforation of the bowel, and, in 5 cases, for no known reason other than previously developed habits.

Results of Present Study

The morbidity rate in each series is shown in Table I. Surgical morbidity rates by the established criteria were 42.3 per cent in the series in which sulfathiazole was used intraperitoneally and there was no vaginal preparation in the operating room (1947), 16.7 per cent in the series in which both sulfathiazole was left in the peritoneal cavity and the vagina was prepared in the operating room (1948), and 23.1 per cent in the series in which the vagina was prepared in the operating room but no sulfathiazole was placed in the peritoneal cavity (1949). The over-all morbidity rate for 323 patients in the three series was 27.2 per cent.

TABLE I. SURGICAL MORBIDITY* OF PATIENTS HAVING TOTAL ABDOMINAL HYSTERECTOMY

YEAR	TOTAL CASES	MORBIDITY	
		NO. CASES	PER CENT
1947	104	44	42.3
1948	102	17	16.7
1949	117	27	23.1
Total	323	88	27.2

*Temperature of 100.4° F. or more on two or more days, excluding day of operation.

Table II gives in detail the occurrence of a temperature of 100.4° F. or higher for patients who underwent total abdominal hysterectomy. It should be noted that 35.6 per cent of patients in 1947, 57.9 per cent in 1948, and 45.2 per cent in 1949 did not have temperatures reaching 100.4° F. during the postoperative course. No patient had a temperature as high as 100.4° F. longer than seven days after operation in 1947, longer than four days in 1948, or longer than six days in 1949.

TABLE II. TEMPERATURE OF 100.4° F. OR HIGHER AFTER TOTAL ABDOMINAL HYSTERECTOMY

DAYS	1947		1948		1949	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
0	37	35.6	59	57.9	53	45.2
1	23	22.1	26	25.5	37	31.6
2	31	29.8	13	12.7	19	16.2
3	7	6.7	3	2.9	3	2.6
4	2	1.9	1	1.0	3	2.6
5	2	1.9	0	0	1	0.9
6	1	1.0	0	0	1	0.9
7	1	1.0	0	0	0	0
Total	104	100.0	102	100.0	117	100.0

A survey of the peak temperature reached after total abdominal hysterectomy (Table III) revealed that the highest postoperative temperature was less than 101.0° F. in 63.4 per cent of patients in 1947, in 82.3 per cent in 1948, and in 74.3 per cent in 1949. A temperature greater than 102.0° F. occurred in 5.8 per cent of patients in 1947, 1.0 per cent in 1948, and 0.9 per cent in 1949. The average peak temperature was 100.7° F. in 1947, 100.4° F. in 1948, and 100.5° F. in 1949.

TABLE III. PEAK TEMPERATURE AFTER TOTAL ABDOMINAL HYSTERECTOMY

TEMPERATURE	1947		1948		1949	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
<99.8° F.	3	2.9	10	9.8	7	5.9
99.8°-100.2° F.	34	32.6	49	48.0	46	39.3
100.4°-100.8° F.	29	27.9	25	24.5	34	29.1
101.0°-101.4° F.	21	20.2	12	11.8	24	20.5
101.6°-102.0° F.	11	10.6	5	4.9	5	4.3
>102.0° F.	6	5.8	1	1.0	1	0.9
Total	104	100.0	102	100.0	117	100.0
Average	100.7°		100.4°		100.5°	

The day of dismissal from the hospital, with the day of operation considered the first postoperative day, for patients having total abdominal hysterectomy, is listed in Table IV. The average postoperative day on which patients were dismissed was 12.0 in 1947, 10.8 in 1948, and 10.6 in 1949. Nine patients (8.7 per cent) in 1947, 7 patients (6.9 per cent) in 1948, and 6 patients (5.1 per cent) in 1949 were dismissed from the hospital on the fifteenth postoperative day or later.

TABLE IV. DAY OF DISMISSAL FROM HOSPITAL AFTER TOTAL ABDOMINAL HYSTERECTOMY

HOSPITAL DAYS	1947		1948		1949	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
6	1	1.0	0	0	1	0.9
7	0	0	1	1.0	5	4.3
8	0	0	6	5.9	5	4.3
9	1	1.0	8	7.8	21	17.9
10	15	14.4	51	50.0	55	47.0
11	41	39.3	16	15.7	13	11.1
12	27	26.0	7	6.9	6	5.1
13	6	5.8	3	2.9	4	3.4
14	4	3.8	3	2.9	1	0.9
15+	9	8.7	7	6.9	6	5.1
Total	104	100.0	102	100.0	117	100.0
Average	12.0 days		10.8 days		10.6 days	

Simultaneous appendectomy was performed in 54.8 per cent of cases in 1947, 49.0 per cent of cases in 1948, and 55.5 per cent of cases in 1949, or in about half of the cases in each series (Table V). The appendix was present but not removed in 5.8 per cent of cases in 1947, in 11.8 per cent of cases in 1948, and in 4.3 per cent of cases in 1949. The difference in 1948 was due to the higher incidence of malignancies and to the fact that in these cases the appendix was not removed routinely. Morbidity in 1948 and 1949 was essentially the same with and without simultaneous appendectomy (Table VI). In the series for 1947, the reason for a morbidity rate of 36.8 per cent in cases with appendectomy, in contrast to a morbidity rate of 48.9 per cent in cases without simultaneous appendectomy, was not evident.

TABLE V. TOTAL ABDOMINAL HYSTERECTOMY AND APPENDECTOMY

	1947		1948		1949	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
Simultaneous appendectomy	57	54.8	50	49.0	65	55.5
Previous appendectomy	41	39.4	40	39.2	47	40.2
Appendix not removed	6	5.8	12	11.8	5	4.3
Total	104	100.0	102	100.0	117	100.0

TABLE VI. EFFECT OF SIMULTANEOUS APPENDECTOMY ON SURGICAL MORBIDITY IN CASES OF TOTAL ABDOMINAL HYSTERECTOMY

	1947			1948			1949		
		MORBIDITY*			MORBIDITY*			MORBIDITY*	
	NO. CASES	NO. CASES	PER CENT	NO. CASES	NO. CASES	PER CENT	NO. CASES	NO. CASES	PER CENT
Simultaneous appendectomy	57	21	36.8	50	8	16.0	65	15	23.1
No simultaneous appendectomy	47	23	48.9	52	9	17.3	52	12	23.1
Total	104	44	42.3	102	17	16.7	117	27	23.1

*Temperature of 100.4° F. or more on any two or more days, excluding day of operation.

Age distribution, a factor in morbidity at times, was determined in each series of cases of total abdominal hysterectomy. The average age of the patients was 44.2 years in 1947, 46.1 years in 1948, and 45.3 years in 1949. In the series for 1947, 5 patients (4.8 per cent) were more than 60 years of age; in 1948, 6 patients (5.9 per cent), and in 1949, 7 patients (5.9 per cent) were in this same category.

Pelvic malignant disease was present in 10 cases (9.6 per cent) in 1947, in 19 (18.6 per cent) in 1948, and in 14 (11.9 per cent) in 1949. Morbidity rates were 60.0, 21.0, and 35.7 per cent, respectively, in the three series. The average number of days spent in the hospital by patients having pelvic malignant diseases was 12.8, 11.3, and 12.7 days, respectively, in the three series. Although the number in each series is small it does reveal the same trend in morbidity as the larger series.

A study was made of all cases in which the patient was considered to be morbid in the postoperative period. Patients with a temperature of 100.4° F. or higher on the second and third postoperative days only, and with no demonstrable cause of the febrile reaction, were considered to have "physiologic" morbidity. "Physiologic" morbidity was present in 27 (61.3 per cent) of the 44 cases of morbidity in the series for 1947, in 11 (64.7 per cent) of the 17 cases for 1948, and in 17 (62.9 per cent) of the 27 cases for 1949. In a number of other cases in which the patient was considered morbid by the standard described previously, elevation of temperature occurred on other than the second and third postoperative days but a cause for the hyperpyrexia was not evident.

Usual postoperative difficulties, such as gastric retention, vaginal bleeding, and thrombophlebitis were encountered infrequently and with approximately equal incidence in each series. Cystitis occurred in many cases, rarely caused morbidity, and usually responded promptly to conservative treatment. Reactions possibly attributable to intraperitoneal use of sulfathiazole occurred in only 2 cases, 1 in 1947 and 1 in 1948. In the first case erythema multiforme was manifested, and in the second case urticaria developed; in each case the disease subsided uneventfully.

Only 1 death occurred, and this was in 1947. Consequently the mortality rate for the 1947 series of 104 cases was 0.96 per cent, and the over-all mortality rate for the entire 323 cases was 0.31 per cent. The patient who died was a woman 48 years of age with severe menorrhagia; the value for hemoglobin was 6.7 Gm. per 100 c.c. of blood on admission, the heart was enlarged and filled the left portion of the thorax, she had hypertension, auricular fibrillation and she was obese. After transfusions, total abdominal hysterectomy was performed, as it was felt she was not a candidate for radium or roentgen therapy as the uterus contained multiple large fibromyomas. On the fifth postoperative day, although the patient was receiving Dicumarol and her prothrombin time was 58 seconds, an embolus to the right popliteal artery occurred. On the sixth postoperative day, in spite of a prothrombin time of 115 seconds, an

embolus reached the left popliteal artery and fifty minutes later the patient died suddenly. Post-mortem examination was not allowed but our clinical impression was that the multiple emboli were from mural thrombi.

During the fourth quarter of 1949, again both vaginal preparation in the operating room before operation and intraperitoneal administration of sulfathiazole were employed. It was interesting to note that, of the 24 cases of total abdominal hysterectomy performed during this period, 4 patients (16.7 per cent) had morbid courses, an incidence identical to the comparable series in 1948; there were no deaths.

Comment

Our study of three series of cases of total abdominal hysterectomy is enlightening and our impressions are contrary to those we maintained prior to the study. Formerly, it was our opinion that the intraperitoneal use of sulfathiazole was the most important factor in lowering morbidity. Our survey, however, clearly shows by every criterion (Tables I, II, and III) that the lowest incidence of morbidity after total abdominal hysterectomy resulted from the use of both vaginal preparation and sulfathiazole in the peritoneal cavity in 1948. Almost as satisfactory results were obtained from the use of vaginal preparation alone in 1949. A much higher morbidity followed the use of intraperitoneal sulfathiazole alone in 1947.

Progressively earlier ambulation was employed in the three series, which is in keeping with recent trends. Earlier ambulation definitely shortened the period of hospitalization during 1949.

These three series consist of comparable groups of cases of total abdominal hysterectomy and findings should be significant, since no known factors except preparation of the vagina, intraperitoneal use of sulfonamides, and earlier ambulation influenced the results.

Summary and Conclusions

Vaginal preparation with soap and water and antiseptic in the operating room before operation is an important factor in lowering surgical morbidity after total abdominal hysterectomy.

Intraperitoneal use of sulfathiazole somewhat lowers morbidity after total abdominal hysterectomy, but it is much less important than vaginal preparation.

Appendectomy performed simultaneously with total abdominal hysterectomy has no effect on morbidity and should be performed in all cases in which there is no contraindication.

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CYTODYNAMIC PROPERTIES OF THE HUMAN ENDOMETRIUM

III. Variations in the Nucleoprotein Content of the Endometrium During the Menstrual Cycle

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BARTELMEZ and Bensley[1] described the presence in the cytoplasm of endometrial gland cells of basophilic, "chromidial-like material" which Wislocki and his co-workers and Atkinson, Engle, Gusberg, and Buxton[2] later identified as ribonucleic acid. The latter workers demonstrated cytochemically that the amount of ribonucleic acid varies during the menstrual cycle, being greatest during the proliferative phase and almost disappearing just before the menses.

The importance of ribonucleic acid in growth and in general cellular metabolism has been stressed recently, but there are no quantitative, chemical data concerning the amounts of desoxyribonucleic acid (DNAP) and ribonucleic acid (RNAP) present in the endometrium. Therefore, a series of experiments was performed to determine the concentrations of DNAP and RNAP present in human endometrium during the different phases of the menstrual cycle.

Material

Endometrium for this study was procured from (a) weekly endometrial biopsies on six regularly menstruating, physically healthy women in the reproductive age, and (b) intact uteri removed surgically from women with regular menstrual histories.

The endometrium was weighed on a Roller-Smith balance, homogenized in ice-cold 10 per cent trichloracetic acid, and treated as described hereafter. The tissue was analyzed for DNAP and RNAP according to a modification of the Schmidt and Thannhauser method.[3]

1. The tissue was homogenized in 5 volumes of 10 per cent ice-cold trichloracetic acid, and transferred quantitatively to a 15 ml. conical centrifuge tube. After standing 15 minutes it was centrifuged. All supernates, which contained the acid-soluble and lipid-soluble compounds, were discarded throughout the entire procedure.
2. The precipitate was suspended in 5 ml. of cold 10 per cent trichloracetic acid and centrifuged. The procedure was repeated.
3. The precipitate was again suspended in 1 ml. cold water and 4 ml. 95 per cent ethyl alcohol were added. After centrifugation the washing was repeated with the use of 5 ml. 95 per cent ethyl alcohol.
4. The precipitate was suspended in 10 ml. of ethyl alcohol-ether mixture (3:1) and placed in water bath at 60° C. for 4 minutes before centrifugation. Step 4 was repeated.

5. Two ml. of 1N potassium hydroxide were added to the precipitate in tube which was placed in a stoppered tube overnight at 37° C., and then made up to exactly 10 ml. with 1N potassium hydroxide.

6. DNAP was precipitated from a 2 ml. aliquot by the addition of 0.5 ml. of ice-cold 6N hydrochloric acid and 4 ml. of ice-cold 5 per cent trichloracetic acid and centrifuged after standing 15 minutes. The precipitated DNAP was washed with 5 ml. ice-cold trichloracetic acid, and centrifuged. The washing was repeated with trichloracetic acid (5 per cent).

7. The phosphorus was determined by the method of Fiske and Subarrow.[4]

8. One ml. aliquots were used for determination of total phosphorus. The wet-ashing for the conversion of organic phosphorus to inorganic phosphorus was accomplished with sulfuric acid and Superoxol (30 per cent hydrogen peroxide). RNAP was determined by subtracting the DNAP from the total nucleic acid phosphorus (NPP) after correction for dilution and aliquot taken.

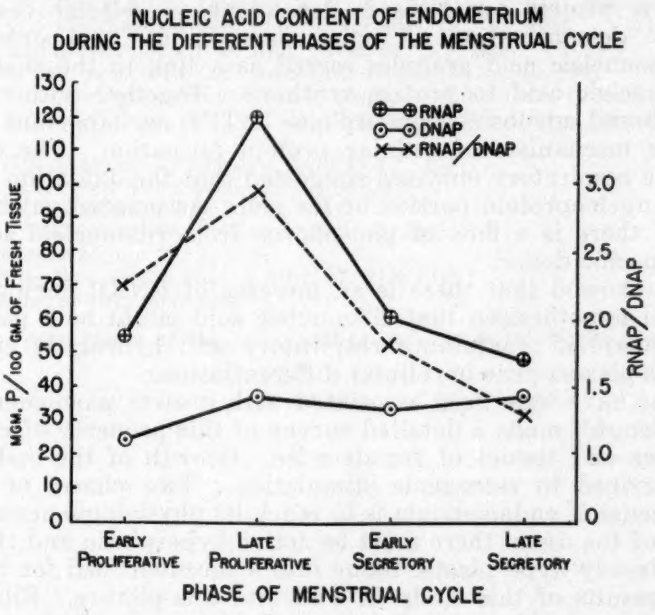

Fig. 1.

The determined concentrations of DNAP and RNAP during the various phases of the menstrual cycle are presented in Table I and Fig. 1. The data show that the amounts of DNAP and RNAP vary during the cycle. During the early proliferative phase averages of 55 mg. RNAP and 25 mg DNAP per 100 Gm. of fresh tissue were found. During the late proliferative phase the average RNAP increased to 120.2 mg. and DNAP to 38 mg. The RNAP content of early and late secretory endometrium was 59.4 and 46.8, respectively, while the corresponding DNAP values were 33 and 36 mg. These values coincide with the cytochemical variations described by Atkinson and associates.[2]

Interpretation of these results depends upon the researches of Casperson,[5] Brachet,[6] and Spiegelman and Kamen,[7] who presented evidence that the ribonucleic acid content is high in rapidly growing tissues and in organs actively synthesizing protein. These findings suggested that structural proteins, enzymes, and secretory products are formed in the presence of ribonucleic acid, and that the RNAP content of a cell provides an index of its rate of protein synthesis.

TABLE I. NUCLEIC ACID CONTENT OF THE ENDOMETRIUM DURING THE MENSTRUAL CYCLE, EXPRESSED AS MILLIGRAMS RIBONUCLEIC ACID PHOSPHORUS (RNAP) AND MILLIGRAMS DESOXYRIBONUCLEIC ACID PHOSPHORUS (DNAP) PER 100 GM. FRESH TISSUE

PHASE OF CYCLE	NPP*	RNAP	DNAP	RNAP/DNAP
Proliferative.—				
a. Early	80.0 (77-83)	55.0 (52-60)	25.0 (23-29)	2.2
b. Late	158.2 (135-164)	120.2 (116-129)	38.0 (36-41)	2.9
Secretory.—				
a. Early	92.4 (88-95)	59.4 (54-65)	33.0 (31-35)	1.8
b. Late	82.8 (79-84)	46.8 (42-51)	36.0 (34-38)	1.3

*Total nucleoprotein phosphorus. Figures in parentheses indicate range.

Obviously, protein synthesis is dependent on cellular respiration; and Chantrenne's[8] demonstration of cytochrome oxidase and succinic dehydrogenase in ribonucleic acid granules served as a link in the chain of evidence joining ribonucleic acid to protein synthesis. Together with these enzymes, Chantrenne found adenosine triphosphate (ATP), an important component in the oxidative mechanism of cellular protein formation. The coexistence of ATP with the respiratory enzymes suggested that the oxidation of ATP could occur in the nucleoprotein portion of the cell. As pointed out by Spiegelman and Kamen,[7] there is a flow of phosphorus from ribonucleic acid with ATP acting as a specific donor.

Brachet[9] showed that there is an increase of RNAP during cellular proliferation and hypothesized that ribonucleic acid might be a part of the "nucleoprotein complex" containing respiratory and hydrolytic enzymes which might act as a plasma-gene in cellular differentiation.

Estrogens have long been associated with growth phenomena in all body tissues. Bullough[10] made a detailed survey of this property of estrogen in the various organs and tissues of female mice. Growth of the endometrium has also been ascribed to estrogenic stimulation. Two phases of growth must occur in sequence if endometrium is to reach its physiologic acme. To prepare for nidation of the ovum there must be active hyperplasia and then specialization of the already hyperplastic tissue into a succulent bed for the implanting ovum. The results of this study fit well into this picture. Ribonucleic acid, a compound inextricably related to growth phenomena, is found most abundantly in the endometrium during the proliferative stage (the phase of estrogenism, of growth, and of differentiation). When sufficient cells have accumulated, their conversion into the future bed for the ovum, into the future source of energy for the implanting egg, and into the chorion-epithelial system of the fetus initiates the stage of specialization.

Interestingly enough, in addition to the diagnostic possibilities of quantitative DNAP and RNAP determinations, particularly in cases of sterility and menstrual disorders, there appears to be a possible therapeutic approach to the same problems. Hertz and co-workers[11, 12, 13, 14] found: (a) that folic acid is required for optimal tissue growth response to estrogens in the genital tracts of female chicks and monkeys; (b) that folic acid antagonists quantitatively inhibit estrogen-induced growth in the genital tracts of female chicks and rats; (c) that such inhibition is reversed by large doses of folic acid; (d) that certain purines and pyrimadines exhibit anti-folic acid activity when tested on bacteria; (e) that 2,6 diaminopurine, an analogue of purine, inhibited the estrogenic response in the genital tracts of female chicks and that this inhibition is largely reversible by adenine, i.e., 6-aminopurine.

Thus, it seems possible that some of the abnormal endometrial patterns seen in gynecologic patients may be due to the influence of substances similar in action to the folic acid antagonists which interfere with nucleoprotein metabolism.

Summary

1. Desoxyribonucleic and ribonucleic acids vary in quantity during the menstrual cycle. The highest values are obtained during the late proliferative phase and the lowest during the late secretory stage.

2. The relationship of nucleic acids to growth, estrogens, and folic acid is discussed.

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(The fourth paper of this series will be included in the March issue.)

CARCINOMA OF THE CERVIX IN JEWISH WOMEN

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PRESENT-DAY emphasis on routine total as opposed to supracervical hysterectomy renews interest in the question of the incidence of carcinoma of the cervix in Jewish women. Although there are some dissenters,[1, 2] most contemporary writers favor total rather than subtotal hysterectomy as a routine procedure when benign disease necessitates the removal of the uterus.[3-7] The principal reason for this is the incidence of carcinoma in the residual stump after subtotal hysterectomy.[8-13] However, many advocates of the total operation will, when performing a hysterectomy on a Jewish woman, allow the cervix to remain because of the alleged rarity of cancer of the uterine cervix in the Jewess, on the grounds that the additional risk, if any, of total hysterectomy is not warranted in this ethnic group. The question arises, "How rare is carcinoma of the cervix in Jewish women?" The present study was undertaken in an attempt to clarify this problem.

Methods and Material

The records of The Mount Sinai Hospital for the past 21 years, from Jan. 1, 1928, to Dec. 31, 1948, were examined to determine the frequency of carcinoma of the cervix in Jewish women. During this 21 year period 323 patients with carcinoma of the cervix were treated on the ward and private services of the Mount Sinai Hospital, 239 of these cases were on the ward and 84 on the private service. Three hundred one patients (93 per cent) had squamous-cell carcinoma of the cervix, while 22 (7 per cent) had adenocarcinoma of the cervix (Table I). With 12 exceptions (patients who had received their original treatment elsewhere) the diagnosis of carcinoma of the cervix in all other cases was made in the pathological laboratories of The Mount Sinai Hospital.

TABLE I. DISTRIBUTION OF CASES ACCORDING TO SERVICE AND HISTOLOGICAL TYPE (MOUNT SINAI HOSPITAL 1928-1948)

	SQUAMOUS	ADENOCARCINOMA	TOTAL
Ward	219	20	239
Private	82	2	84
Total	301	22	323

As patients admitted to the Mount Sinai Hospital are not routinely questioned as to their religion, it was somewhat of a problem to determine the number of Jewish patients in this group. Fortunately, in many instances this information was recorded on the hospital chart by examiners who were familiar with the reputed rarity of this lesion in Jewish patients. In the vast majority of the ward patients, information as to their religion was made available to us

by the Social Service Department which maintained an intimate personal relationship with them throughout the course of their disease. In the private group, this information was obtained by writing to the private physicians. In a few instances, it was necessary to write to other hospitals where the individual concerned was hospitalized before or after admission, or to see the patients in our follow-up clinic or contact their families. In the 14 cases (8 ward, 6 private) where it was not possible to obtain a definite statement as to the religion, the patient was classified as not Jewish.

Results

Of the 323 patients included in this report, 80 (25 per cent) were Jewish and 243 (75 per cent) were not Jewish. Of the 80 Jewish patients with carcinoma of the cervix, 50 were ward and 30 were private patients. Eight (10 per cent) had adenocarcinoma, while 72 had squamous-cell carcinoma (Table II).

TABLE II. DISTRIBUTION OF CASES ACCORDING TO RELIGION
(MOUNT SINAI HOSPITAL 1928-1948)

	SQUAMOUS		ADENOCARCINOMA		TOTAL	
	JEWISH PATIENTS	NON-JEWISH PATIENTS	JEWISH PATIENTS	NON-JEWISH PATIENTS	JEWISH PATIENTS	NON-JEWISH PATIENTS
Ward	42	177	8	12	50	189
Private	30	52	0	2	30	54
Total	72	229	8	14	80	243

There were 8 Jewish patients with carcinoma of the cervical stump following subtotal hysterectomy. Seven of these had squamous-cell carcinoma, 6 of which cases occurred 4 or more years after the subtotal hysterectomy, and 1 of which occurred six months after operation. There was one case of adenocarcinoma of the cervical stump occurring 2 years after the operation. Therefore, 6 cases can be classified as true carcinomas of the cervical stump.

Incidence

The estimated number of women admitted to the ward and private services of the Mount Sinai Hospital during the 21 year period under consideration was 145,268. As there were 323 patients with carcinoma of the cervix during this period, the incidence of carcinoma of the cervix at this hospital is determined as 2.2 per 1,000 women admitted to the hospital.

As mentioned above, patients are not routinely questioned as to their religion on admission to the Mount Sinai Hospital. However, once a year a spot check of 250 to 1,000 consecutive ward admissions is made to determine the percentage of Jews admitted. The sample checked was about one-thirtieth of the total number of admissions. No such check is made on the private and semi-private services. Therefore, in calculating the relative incidence of carcinoma of the cervix in the Jewish as compared to the non-Jewish woman, we must confine ourselves to the figures available for ward patients only.

The number of women admitted to all the ward services during the period under consideration is 98,996. Of these an estimated 58.5 per cent, or 57,912, were Jews and 41,084 were non-Jews. On the ward service, as previously stated, there were 50 Jewish patients and 189 non-Jewish patients with carcinoma of the cervix. The incidence of carcinoma of the cervix in the two groups is, therefore, 0.86 per 1,000 women admitted to the hospital in the Jewish group, and 4.6 per 1,000 women admitted in the non-Jewish group (Table III).

The ratio of the incidence of cancer of the cervix in the non-Jewish woman to the incidence of cancer of the cervix in the Jewish woman is, therefore, 4.6 divided by 0.86, or 5.34. Thus carcinoma of the cervix is about one-fifth as common in the Jewish woman as in the non-Jewish woman as seen in our material.

TABLE III. INCIDENCE OF CANCER OF THE CERVIX IN WARD PATIENTS ACCORDING TO RELIGION (MOUNT SINAI HOSPITAL 1928-1948)

	NUMBER OF CASES	NUMBER OF WOMEN ADMITTED	INCIDENCE (PER 1,000 WOMEN ADMITTED TO HOSPITAL)
Jewish patients	50	57,912	0.862
Non-Jewish patients	189	41,084	4.60

$$\frac{\text{Incidence of cancer of the cervix in the non-Jewish woman}}{\text{Incidence of cancer of the cervix in the Jewish woman}} = 5.34$$

TABLE IV. ESTIMATED INCIDENCE OF CANCER OF THE CERVIX ACCORDING TO RELIGION (BELLEVUE HOSPITAL 1925-1945)

	NUMBER OF CASES (1925-1945)	PER CENT OF ADMISSION (1948)	ESTIMATED NUMBER OF ADMISSIONS (1925-1945)	INCIDENCE (PER 1,000 HOSPITAL ADMISSIONS)
Jewish patients	25	10.18%	127,944	0.196
Non-Jewish patients	1317	89.82%	1,128,874	1.17

$$\frac{\text{Incidence of cancer of the cervix in the non-Jewish woman}}{\text{Incidence of cancer of the cervix in the Jewish woman}} = 5.9$$

Note.—In comparing Table III with Table IV please note that in the former the incidence is calculated per 1,000 *women* admitted to the hospital, while in the latter the incidence is per 1,000 hospital admissions (men and women, including newborn infants). The differences in the absolute incidences quoted in these two tables is further explained by the fact that the make-up of the hospital populations of the two institutions is somewhat different. Some types of cases (emergency, psychotic, tuberculous, etc.) which are admitted to Bellevue Hospital in large numbers are rarely admitted to the Mount Sinai Hospital.

Comment

This figure for the relative incidence of carcinoma of the cervix in the Jewish as compared to the non-Jewish woman is very similar to that estimated by Davidsohn[14] in 1939 at the Mount Sinai Hospital, Chicago, on the basis of a small series of cases. According to our data, the incidence of carcinoma of the cervix in the Jewish woman is more common than found by Vineberg[15] and Rubin.[16] The former was the first to investigate this problem, on the basis of 18 cases seen in the outpatient department of the Mount Sinai Hospital, New York (1893-1906). He determined that carcinoma of the cervix is 19 times more common in the non-Jewish woman than in the Jewish woman. Rubin, on the basis of 85 cases seen in the outpatient department and on the wards of the Mount Sinai Hospital, New York (1909-1918), found that carcinoma of the cervix is 12.5 times more common in the non-Jewish woman than in the Jewish.

It is unfortunate that neither Smith,[17] who in 1937 reported a series of 3,106 patients with carcinoma of the cervix from the Memorial Hospital, N. Y., of whom 132 were Jewish, nor Kaplan and Rosh,[18] who reported on 25 Jewish patients in a series of 1,342 admissions for carcinoma of the cervix at Bellevue Hospital, New York, furnished data on the make-up of the hospital population from which one could calculate the relative incidence of carcinoma of the cervix in Jewess and non-Jewess. However, we were able to obtain the figures for the total number of admissions and the total number of Jewish patients admitted

to Bellevue Hospital for one year only, 1948. If, simply for the purpose of comparison with the results obtained at the Mount Sinai Hospital, we make the assumption that the same percentage of Jews admitted to Bellevue Hospital holds for the entire twenty-one-year period during which Kaplan and Rosh collected their series of patients as for the year 1948, we may calculate the relative incidence of cancer of the cervix between non-Jewish and Jewish women in Kaplan and Rosh's series as follows. During this year 54,860 patients were admitted to Bellevue Hospital. Of these, 5,586 patients were Jewish according to the data recorded on each admission card by the admitting clerk. Thus, 10.18 per cent of those admitted were Jewish patients. Of Kaplan and Rosh's 1,342 patients with cancer of the cervix, collected over a period of 21 years, 25, or 1.86 per cent, were Jewish. During this period (1925-1945) there were a total of 1,256,818 admissions to Bellevue Hospital. By a simple arithmetical calculation as shown in Table IV, we find that at Bellevue Hospital, cancer of the cervix is 5.9 times as common in the non-Jewish woman as in the Jewish woman. This result agrees remarkably with that obtained from the records of the Mount Sinai Hospital.

Some recent reports on the racial incidence of carcinoma of the cervix have pictured the occurrence of the lesion in a Jewish woman as a rarity. In an analysis of 568 consecutive cases at the Mayo Clinic, Treusch and associates[19] found no patient whose religious preference was definitely stated as being Jewish. Similarly Maliphant[20] found no Jewish women among 1,200 patients with carcinoma of the cervix in Cardiff, Wales. The striking absence of Jewish women from these and other series of patients with carcinoma of the cervix, probably reflects the low incidence of Jews in the population from which these patients were drawn. That carcinoma of the cervix occurs in Jewish women more frequently than would be surmised from these reports is evident from the figures that we and other authors have presented.

The exact incidence of cancer of the uterine cervix is difficult to ascertain statistically.[21] Foote and Lie,[22] quoting from the Department of Statistics, Memorial Hospital, New York, and the New York State Division of Cancer Control, have estimated the incidence of carcinoma of the cervix in women over 35 years of age as 1 in 1,500. Applying our figure that carcinoma of the cervix is 5.34 times as common in the non-Jewish woman as in the Jewish woman, and realizing that Jews are in a small minority, one may estimate the incidence of carcinoma of the cervix in Jewish women over 35 years of age as approximately 1 in 8,000. Morris and Meigs[21] quote the New York State Department of Health to the effect that the probability of a woman developing cancer of the cervix from birth to death is 2.196 per cent. Applying our result as to the relative incidence of carcinoma of the cervix, we may estimate that the probability of a Jewish woman developing cancer of the cervix from birth to death is 0.41 per cent.

There have been many theories proposed for the difference in incidence of carcinoma of the cervix between Jewish and non-Jewish women. Sorsby[23] and Vineberg[15] felt that the limitation of cohabitation during the menstrual period as imposed by the Mosaic laws is an important factor in limiting irritation and subsequent carcinoma of the cervix in the Jewess. Horowitz[24] emphasized the importance of the ritual dietary laws. A comparison of Davidsohn's[14] and our figures for the incidence of carcinoma of the cervix in the Jewish woman as compared to the non-Jewish woman, with those of Vineberg[15] and Rubin[16] seems to indicate an increasing occurrence of carcinoma of the cervix in Jewish women. This apparent increase lends support to Vineberg's theory, as the Jewish women of today do not adhere as meticulously to the Mosaic laws as they did at the turn of the century. Davidsohn[14] feels that the

difference in incidence may be explained by the practice of circumcision in the Jewish male, and supports his argument by noting the infrequency of this same form of malignancy among the Mohammedans of India who also practice circumcision of all males. Further support is given to Davidsohn's theory by the demonstration of the carcinogenic action of smegma by Plaut and Kohn-Speyer.[25] The factor of hereditary immunity probably plays a role.

Summary

1. Of 323 patients with carcinoma of the cervix seen at the Mount Sinai Hospital, New York, from 1928 to 1948, there were 80 Jewish women. Eight of these patients had carcinoma of the cervical stump following subtotal hysterectomy.

2. Carcinoma of the cervix in Jewish women, although not common, is not a rare lesion. Carcinoma of the cervix occurs about five times as frequently in the non-Jewish as in the Jewish woman.

We express our deep appreciation and thanks to Dr. William Harris of the Mount Sinai Hospital for his advice and encouragement in the preparation of this paper, and for the permission to use the records of his private patients. We also wish to express our thanks to the many members of the staff who allowed us to review the records of their private patients, and to Miss Ethel Weinstein of the social service department who was of invaluable assistance in determining the religious status of most of these patients. Dr. Hyman Krakauer, Visiting Lecturer in Biostatistics, Department of Preventive Medicine, New York University College of Medicine, rendered invaluable assistance in reviewing the statistical material.

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THE SUBSEQUENT COURSE OF PATIENTS STERILIZED BY TUBAL LIGATION

A Consideration of Hysterectomy for Sterilization

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AMONG the more frequent operations performed in gynecology is that of sterilization by interruption of the continuity of the Fallopian tubes. Many physicians accept a wide variety of indications for this operation, but others either do not perform the operation or reserve it for individuals with very grave systemic or pelvic abnormalities. Uniform success in preventing future pregnancies has been obtained by any one of a number of operative techniques designed to obstruct or disrupt permanently the patency of the oviducts. Although much information is available as to the indications for the operation and the success of the various techniques, relatively few data are to be found regarding the subsequent course of these patients.

Material

The incidence of the development of subsequent pelvic disorders has been tabulated in the 200 patients upon whom tubal sterilization procedures were carried out on the ward service of the Vanderbilt University Hospital from 1926 through 1948. Table I indicates the occurrence and frequency of the pelvic disturbances found in these 200 individuals following the sterilization operation. Only abnormalities of a significant degree are included. Minor bleeding disorders and all diseases of the cervix are excluded.

TABLE I

PELVIC DISORDER	NUMBER OF PATIENTS
Menorrhagia	26
Metrorrhagia	4
Myoma	10
Pelvic inflammatory disease	4
Endometriosis	2
Adenomyosis	1
Carcinoma of endometrium	1
Total	48

Note.—If more than one of the above disorders occurred in the same patient, only the most significant was listed.

It should be noted that the 48 patients in Table I who subsequently were found to have pelvic disorders number 24 per cent of the total 200 patients, and that this is undoubtedly a minimal figure because of the fact that several of the 200 patients failed to return for follow-up, and many had only a few months of follow-up. A statistical analysis, taking into account differences in

the length of time which has elapsed since the sterilization operation, has been carried out on the 200 patients to determine the frequency with which significant pelvic disorders would be expected to occur during a ten-year follow-up period. Since the percentage of patients developing pelvic disorders is dependent upon the length of the observation period, which ranged from a few months to 22 years, an analysis has also been carried out to determine the frequency of occurrence of such disorders during each of the first ten years of observation. In Table II the percentage of patients expected to develop disorders during a ten-year follow-up period has been derived by the usual "life table" method of analysis.[1]

TABLE II. TOTAL PATIENTS

YEARS AFTER OPERATION	AVERAGE NUMBER UNDER OBSERVATION DURING YEAR	NUMBER KNOWN TO DEVELOP COMPLICATIONS DURING YEAR	PER CENT DEVELOPING COMPLICATIONS DURING YEAR	CUMULATIVE PER CENT DEVELOPING COMPLICATIONS IN CURRENT AND PRECEDING YEARS
0- 1	196.0	16	8.2	8.2
1- 2	169.5	4	2.4	10.4
2- 3	152.5	4	2.6	12.7
3- 4	136.5	5	3.7	15.9
4- 5	120.5	5	4.1	19.3
5- 6	106.5	4	3.8	22.4
6- 7	94.5	4	4.2	25.7
7- 8	83.5	4	4.8	29.3
8- 9	74.0	1	1.4	30.3
9-10	64.0	1	1.6	31.4

Interest centers in the last column of Table II which gives the estimated percentage of patients developing pelvic disorders within one year, two years, etc., after operation. According to the table, about 31 per cent of a group of patients will have developed complications within ten years after operation. This is probably a minimum figure. The incidence of pelvic disorders was somewhat lower in patients under 35 years of age at the time of sterilization operation (Table III) than in patients over 35 years of age (Table IV), but the difference is not great.

TABLE III. PATIENTS UNDER 35 YEARS OF AGE

YEARS AFTER OPERATION	AVERAGE NUMBER UNDER OBSERVATION DURING YEAR	NUMBER KNOWN TO DEVELOP COMPLICATIONS DURING YEAR	PER CENT DEVELOPING COMPLICATIONS DURING YEAR	CUMULATIVE PER CENT DEVELOPING COMPLICATIONS IN CURRENT AND PRECEDING YEARS
0- 1	130.5	8	6.1	6.1
1- 2	116.5	2	1.7	7.7
2- 3	107.0	3	2.8	10.3
3- 4	97.5	4	4.1	14.0
4- 5	88.0	5	5.7	18.9
5- 6	78.5	3	3.8	22.0
6- 7	71.5	1	1.4	23.1
7- 8	65.5	4	6.1	27.8
8- 9	57.5	1	1.7	29.0
9-10	50.0	0	0.0	29.0

In an effort to evaluate the significance of the high percentage of pelvic abnormalities occurring in this series of patients following sterilization, the punch card records of 3,222 obstetrical patients hospitalized during the years 1942 through 1944, and 1,994 gynecological patients hospitalized during the

years 1942 through 1948 were examined. Any past history of increased duration or increased amount of vaginal bleeding was noted. Of the 3,222 obstetrical cases 5.1 per cent gave a past history of abnormal bleeding. Of the 1,994 gynecological cases 19.1 per cent gave a past history of abnormal bleeding. Significant abnormal bleeding is known to have occurred in 16.5 per cent of the 200 poststerilization cases. Because of the lack of long-term follow-up in many instances, and no follow-up in some, it would be expected that more abnormal bleeding would be disclosed had these patients been followed for a length of time comparable to the period reflected in the "past history" of the routine obstetrical or gynecological case history. Even so, the incidence of 16.5 per cent more than triples that of 5.1 per cent found in the obstetrical case histories, the latter probably being a fair indication of the occurrence of bleeding abnormalities in the general female population.

TABLE IV. PATIENTS 35 YEARS OF AGE AND OVER

YEARS AFTER OPERATION	AVERAGE NUMBER UNDER OBSERVATION DURING YEAR	NUMBER KNOWN TO DEVELOP COMPLICATIONS DURING YEAR	PER CENT DEVELOPING COMPLICATIONS DURING YEAR	CUMULATIVE PER CENT DEVELOPING COMPLICATIONS IN CURRENT AND PRECEDING YEARS
0- 1	65.5	8	12.2	12.2
1- 2	53.0	2	3.8	15.5
2- 3	45.5	1	2.2	17.4
3- 4	39.0	1	2.6	19.5
4- 5	32.5	0	0.0	19.5
5- 6	28.0	1	3.6	22.4
6- 7	23.0	3	13.0	32.5
7- 8	18.0	0	0.0	32.5
8- 9	16.5	0	0.0	32.5
9-10	14.0	1	7.1	37.3

Comment

The data presented above suggest that individuals who are subjected to sterilization procedures later develop a higher percentage of abnormal uterine bleeding than would be expected in a comparable number of unselected normal women. It seems most likely that this predisposition to abnormal bleeding is related to the underlying disease or condition for which the sterilization is performed rather than to any mechanical interference with ovarian or uterine function resulting from the operative procedure. Some evidence may be found in the literature in verification of this assumption, especially with reference to the profound constitutional disorders such as hypertension, renal disease, and heart disease. It is of interest to note that approximately one-third of the hypertensive patients in this series developed abnormal bleeding after sterilization.

It is apparent that the pelvic disorders listed in Table I would have been prevented by hysterectomy. Known hysterectomy was performed on five patients in this series subsequent to sterilization, and it may be that other hysterectomies were done at other hospitals among the patients who had limited follow-up.

According to the statistics presented it seems evident that consideration should be given to a preferential performance of hysterectomy, ideally total, rather than a simple interruption of the continuity of the oviducts. Additional consideration is warranted by the fact that in many of these patients the optimum time for the performance of any operative procedure is the time at which sterilization is done. Future surgical procedures that could have been obviated

by hysterectomy may become necessary at a time when the condition of the patient would make these procedures hazardous, not only because of the factor of advancing age, but also because of the progression of the original disease for which sterilization was done. It should be realized that profuse uterine hemorrhage becomes a much greater problem in a patient with, for example, cardiac disease or diffuse pulmonary disease, and it seems logical to attempt to prevent such complications. As far as is known, the uterus plays no important part in the female endocrine function, and its salvage after removal of the reproductive possibilities by tubal interruption probably serves only the purpose of preserving a site from which menstrual bleeding can occur. The preservation of the latter function merits consideration only in the few patients in whom psychic repercussions are likely to follow cessation of menstrual bleeding.

Progressive improvement in operative techniques and preoperative and postoperative care of surgical patients has resulted in a marked reduction of both morbidity and mortality in patients subjected to abdominal hysterectomy. The majority of individuals who are candidates for sterilization procedures possess normal pelvic anatomy, the presence of which should bring the hysterectomy morbidity and mortality to a minimum. It is felt that in the hands of a competent pelvic surgeon there should be little additional hazard in the performance of hysterectomy rather than tubal interruption, once the patient is anesthetized and the abdomen opened.

Summary

1. A high percentage of individuals subjected to tubal interruption for purposes of sterilization at the Vanderbilt University Hospital subsequently developed pelvic abnormalities, the most frequent symptom being abnormal uterine hemorrhage. Comparison with the past histories of a large number of unselected hospitalized obstetrical and gynecological patients indicates the occurrence of bleeding complications to be high and out of proportion to that expected in the general female population. It is our impression that the frequently present systemic disease for which sterilization is performed is causative, rather than any mechanical interference with function resulting from the operative procedure itself.

2. The increased operative risk from the progression of systemic disease and advancing age suggests that the optimum time for any surgical procedure in these patients lies in the present and not in the future.

3. In view of the very low mortality and morbidity resulting from simple hysterectomy in the absence of distortion of pelvic anatomy, it is our impression that hysterectomy rather than tubal interruption should be considered in those individuals with chronic or progressive diseases warranting destruction of the reproductive function. Procedures short of hysterectomy preserve only the menstrual function of the uterus and leave an organ that is, as far as is known, not only worthless but potentially dangerous.

The authors wish to express appreciation to Dr. Margaret Martin of the Department of Preventive Medicine, Vanderbilt University School of Medicine, for aid in the collection and compilation of the statistical data included in this paper.

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RELIABILITY OF THE COPPER SULFATE METHOD AND OTHER ANEMIA TESTS IN PREGNANCY

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THE reliability of the copper sulfate falling drop test in pregnancy will be demonstrated by comparing it with three other simultaneously performed tests for anemia. The hematocrit (packed red cell volume), Sahli, photoelectric-cell colorimeter, and copper sulfate tests will be contrasted for consistency in results.

The author has recorded experiences with several thousand copper sulfate tests in prenatal clinics, reporting the incidence of anemia in 1,669 rural southern women.[1] The copper sulfate test is a simple procedure that can be done by a technically untrained person. The only equipment needed are the copper sulfate solution and the means for collecting a drop of venous or capillary blood. The outcome depends on the rise or fall of a drop of whole blood in a copper sulfate solution of selected specific gravity. With one solution the anemic can be screened from the nonanemic. A series of solutions of graded specific gravities will make the test more quantitative. The greatest usefulness of the test is probably as a rapid screening test. The test has been described in detail elsewhere.[2] Because of the alteration in specific gravity of blood in pregnancy a question has been raised as to the dependability of the test. In the nonpregnant the accuracy of the test seems assured.

Attention has been called by Ham[3] to the inconsonance of hematological laboratory results. Twenty medical students with considerable training performed ten different examinations with the same specimen of blood. The error in the hematocrit and the photoelectric-cell colorimeter method of measuring hemoglobin was small; the results were reproducible within ± 5 per cent because of the inherent small chance of objective and subjective errors. Recognition of the superiority of these two techniques is not new. The Sahli and other determinations compared unfavorably. The red cell count fared so badly it could not be recommended as a routine screening procedure for anemia. A study of the quantitative significance of some of the anemia tests commonly used in prenatal clinics seemed desirable to the present author.

Plan of Study

An attempt was made to test by copper sulfate, Sahli, hematocrit, and photoelectric-cell colorimeter all of the women attending a prenatal clinic at the South Mississippi Charity Hospital, Laurel, Miss. This clinic was jointly operated by the hospital, Tulane University School of Medicine, and the Mississippi State Board of Health. The work was completed in about three months. The Sahli test was done with capillary blood and the other three tests were performed simultaneously with the same specimen of venous blood. Testing was usually carried out on the first prenatal visit. The distribution by month of pregnancy is shown in Table I. There were relatively few tests done in the first, second, third, and ninth months of pregnancy and no preponderance appeared in any period of pregnancy. Because of equipment failures the set of four tests was

completed on only 167 women out of 187 Sahli, 167 colorimeter, 167 hematocrit, and 188 copper sulfate tests. This is a sum of 709 tests on 188 women. Comparisons will be made in this study only with the 167 women who had all four tests. For hematocrit the Wintrobe method was used. The photoelectric-cell colorimeter was a Hellige-Diller. In copper sulfate testing, a solution of specific gravity 1.047, equivalent to 10 Gm. hemoglobin per 100 ml., was used.

TABLE I. DISTRIBUTION OF CASES BY MONTH OF PREGNANCY

MONTH	1	2	3	4	5	6	7	8	9	UNKNOWN
No. patients	1	3	10	17	21	31	29	31	15	9

Several standards have been suggested for deciding who is anemic in pregnancy. The choice in hematocrit may be 30 per cent, 31 per cent, 32 per cent, or, most acceptable probably, 33 per cent. A hemoglobin level of 10 Gm./100 ml., rather than higher values, has received a great deal of acceptability as the minimum figure. In this study any reading below 10 Gm./100 ml. is considered evidence of anemia. Comparison will be made between 10 Gm. and several hematocrit standards. No allowance will be made for decrease in plasma volume in the last weeks of pregnancy.

Comparison of the Tests

Table II shows the distribution of all of the 167 cases by hematocrit and compares them with the copper sulfate, colorimeter, and Sahli readings. Unfortunately, the classification of a patient as anemic seems to depend to a large degree on the choice of test (Fig. 1). By colorimeter 53 patients (31.7 per cent) were anemic, by Sahli 38 (22.8 per cent), and by the copper sulfate test, 31 (18.6 per cent). To state the confusion another way, the colorimeter classified 26 women as anemic who were not anemic by Sahli and the Sahli found 11 patients that the colorimeter missed. The still too common practice of expressing hemoglobin in per cent can be counted on to increase this inconstancy, particularly when results in one laboratory are compared to those in another.

Of course, the number found anemic by hematocrit varied with the level chosen. Under 33 per cent hematocrit there were 25 cases (15 per cent); under 32 per cent hematocrit, 16 cases (9.6 per cent); under 31 per cent hematocrit, 6 cases (4 per cent), and only 4 cases under 30 per cent hematocrit.

Using 33 per cent hematocrit as the minimum accepted level, 16 women were anemic by all four tests, 7 women by three tests, 16 women by two tests and 30 women by one test. If 30 per cent hematocrit had been selected only 4 patients would have been anemic by all four tests.

TABLE II. DISTRIBUTION OF 167 NORMAL AND ANEMIC WOMEN BY FOUR TESTS

	COPPER SULFATE							
	ANEMIC				NORMAL			
	COLORIMETER				COLORIMETER			
	ANEMIC		NORMAL		ANEMIC		NORMAL	
	SAHLI		SAHLI		SAHLI		SAHLI	
HEMATOCRIT	ANEMIC	NORMAL	ANEMIC	NORMAL	ANEMIC	NORMAL	ANEMIC	NORMAL
33% and over	3	4	1	2	13	17	4	98
32%	5			2	1	1		
31%	5	3						1
30% and under	6							

If 30 per cent hematocrit, instead of 33 per cent, had been acceptable in this group of 167 women the following patients would have been considered not anemic: 18 women with colorimeter readings below 9.5 Gm.; 7 women with readings below 8.5 Gm.

PER CENT FOUND ANEMIC BY VARIOUS TESTS AND STANDARDS.

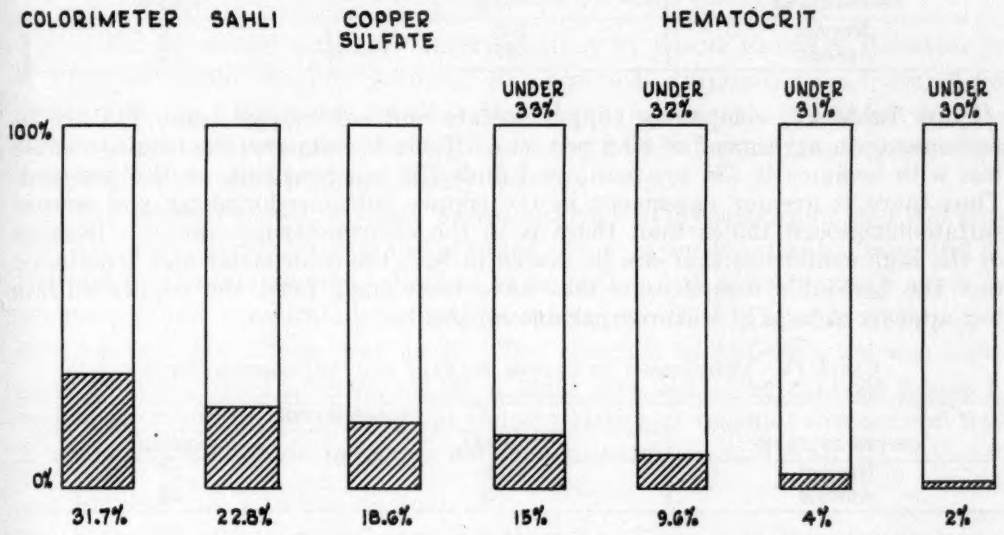

Fig. 1.

These comparisons of various levels of hematocrit and three hemoglobin screening tests place some doubt on the validity of considering 30 per cent hematocrit acceptable in pregnancy, as is the practice in some clinics. The anemia portions of the columns in Fig. 1 seem to indicate that the use of 33 per cent hematocrit as a critical figure is closer to the usual concept of what constitutes anemia in pregnancy.

Reliability of the Copper Sulfate Test

The copper sulfate test appears to be a comparatively rough test, if simplicity and roughness are the same. The following findings seem to establish the copper sulfate method as a satisfactory screening test in pregnancy.

1. If 33 per cent hematocrit as the minimum normal is used for the standard there were 25 women with anemia and the copper sulfate test missed 4 of them (Table II). Of these 4, 3 were not anemic by one or two of the other tests (Sahli and colorimeter) and the fourth had hemoglobin values of 9 and 9.4 Gm./100 ml. The colorimeter, comparable to the hematocrit in dependability, missed three cases, also borderline anemias.

2. Using the colorimeter as the standard, 53 women were found anemic, and the copper sulfate test missed 27 of these cases. However, of these 27 women only 3 had hematocrits below 33 per cent (32 per cent, 32 per cent, 31 per cent).

3. Viewed from the "false anemic" side, there were 7 cases that the copper sulfate test designated as anemic and in which the hematocrit was found to be

33 per cent or greater. Five of these 7 cases had hemoglobin determinations below 10 Gm./100 ml. by one or both of the other tests.

4. The results with hematocrit and colorimeter, the two tests with reputations for reliability, are compared in Table III. One hundred five women were not anemic by both tests and 22 were anemic by both tests, making 127 in agreement, a 76.0 per cent agreement.

TABLE III. COMPARISON OF HEMATOCRIT AND COLORIMETER TESTS

COLORIMETER	HEMATOCRIT	
	33%	<33%
Normal	105	3
Anemic	37	22

In Table IV, comparing copper sulfate and colorimeter tests, 135 are in agreement, an agreement of 80.8 per cent. Table V compares the copper sulfate test with hematocrit (33 per cent) and finds 153 in agreement, or 91.6 per cent. Thus there is greater agreement in the copper sulfate-colorimeter and copper sulfate-hematocrit tables than there is in the colorimeter-hematocrit. Because of the high confidence that can be placed in both the colorimeter and hematocrit and the favorable comparisons that have been made here, the copper sulfate test appears to be of at least comparable reliability.

TABLE IV. COMPARISON OF COPPER SULFATE AND COLORIMETER TESTS

COPPER SULFATE	COLORIMETER	
	NORMAL	ANEMIC
Normal	109	27
Anemic	5	26

TABLE V. COMPARISON OF COPPER SULFATE AND HEMATOCRIT TESTS

COPPER SULFATE	HEMATOCRIT	
	33%	<33%
Normal	132	4
Anemic	10	21

Conclusions

The copper sulfate falling drop test for anemia compares favorably in accuracy with the hematocrit and photoelectric-cell colorimeter tests and is recommended for the screening of pregnant women. The copper sulfate, hematocrit, Sahli, and colorimeter tests differ considerably in their sensitivity as screening tests. Thirty-three per cent hematocrit as the minimum acceptable figure in pregnancy may be more accurate than lower figures.

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A major share of the laboratory work was performed by G. O. Runnels and V. McRaney, Jr., students at the University of Mississippi School of Medicine.

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INCIDENCE AND EFFECTS OF VASCULAR DISEASE IN 1,000 CONSECUTIVE PREGNANCIES IN PRIVATE PRACTICE

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In A recent paper[1] entitled "Interpretation of Blood Pressure Behavior in Pregnancy and the Puerperium," the principal differentiating features between vascular disease and true toxemia of pregnancy were presented, and the value of ophthalmoscopic examination in the recognition of these outstanding causes of hypertension in pregnancy was emphasized.

The present paper is based on an analysis of hypertension in 1,000 consecutive pregnancies in private practice, from seven months to term and to the end of the puerperium. Retinal examination was done routinely early in pregnancy and constituted the sole means by which a diagnosis of latent or existing vascular disease was made. The criterion of hypertension was based on a diastolic blood pressure of 80 or more mm. Hg. The analysis serves to emphasize many of the differential characteristics of vascular disease and true toxemia as presented in the paper above mentioned.

Incidence of Vascular Disease.—

Since the normal arteriovenous ratio is 2 to 3, the mildest or latent degree of vascular disease is represented by a ratio of 2:3 to 1:2. This degree of disturbance in ratio is usually accompanied by a slight increase in light reflex of the retinal arterioles but no arteriovenous compressions.

As may be seen from Table I, this group of cases of mild or latent vascular disease comprised 90 of the 107 cases of vascular disease, and can be recognized only by retinal examination, or possibly by the cold pressor test. This degree of vascular disease is too mild to give rise to significant symptoms or findings prior to pregnancy, but is apparently aggravated by pregnancy to such a degree that it causes a moderate rise of blood pressure to 130 to 140 systolic and 80 to 90 diastolic in the ninth month of pregnancy.

Upon recognizing these minimal arteriolar changes in the retina early in pregnancy, one may quite accurately predict (Table IV) that development of a mild degree of hypertension and a trace of proteinuria will occur in the ninth month of pregnancy. While it is reassuring to know the hypertension is not that of true toxemia, these findings call for greater watchfulness to detect evidences indicating development of a superimposed toxemia, to which patients with vascular disease are so greatly predisposed.

Moderate vascular disease is represented by an arteriovenous ratio of 1:2 to 1:3 and was found in 16 of the 107 cases of vascular disease. In this group the light reflex is definitely increased and an occasional arteriovenous compression may be found, causing the vein to be compressed and distended peripheral to the point where the more rigid arteriole crosses it. In these cases, the systolic and diastolic pressures, though usually normal, may tend to be at the upper limits of normal prior to and early in pregnancy and a significant rise does not begin until the eighth and ninth months.

Severe vascular disease, represented by an arteriovenous ratio of 1:3 to 1:4, was found in only one of the 107 cases of vascular disease. In this group, the light reflex is greatly increased and arteriovenous compressions are frequently found. The blood pressure, both systolic and diastolic, is usually elevated prior to pregnancy and the patient, when first seen early in pregnancy is not considered a safe risk, inasmuch as the blood pressure will usually increase to dangerous levels before the baby reaches viability. Furthermore, the risk of superimposed toxemia is too great.

TABLE I. INCIDENCE OF VASCULAR DISEASE IN 1,000 CONSECUTIVE PREGNANCIES, 7 MONTHS TO TERM IN PRIVATE PRACTICE

	NUMBER	PER CENT
Mild vascular disease A-V ratio 2:3 to 1:2	90	9
Moderate vascular disease A-V ratio 1:2 to 1:3	16	1.6
Severe vascular disease A-V ratio 1:3 to 1:4	1	.1
Total vascular disease	107	10.7

Influence of Age.—

Among the patients free of vascular disease, but developing primary true toxemia, 60.8 per cent were 15 to 24 years of age, 30.5 per cent were 25 to 34 years of age, and 8.7 per cent were 35 to 44 years of age. This agrees with the generally accepted opinion that the young are more subject to primary true toxemia.

Among the patients with vascular disease, mild, moderate and severe, 26.1 per cent were 15 to 24 years of age, 52.3 per cent were 25 to 34 years of age, and 21.5 per cent were 35 to 44 years of age.

While no figures are at present available to show the frequency of vascular disease among Negro patients of the charity service at Grady Memorial Hospital of Atlanta, it is our impression that the incidence is several times higher than that among white patients and contributes considerably to maternal and fetal mortality through increased cardiac and renal disease as well as superimposed toxemia with attendant prematurity and fetal mortality.

Incidence of Superimposed Toxemia.—

Table II indicates that superimposed toxemia occurred in 10.2 per cent of the cases of vascular disease.

TABLE II. INCIDENCE OF SUPERIMPOSED TOXEMIA IN 107 CASES OF VASCULAR DISEASE

	PRE-ECLAMPSIA			ECLAMPSIA	ABRUPTIO
	MILD	MOD.	SEVERE		
Mild vascular disease	5			2	1
Moderate vascular disease	3				
Severe vascular disease	One case; pregnancy interrupted at 7th wk.				
Total*	8			2	1

*Total of 11 cases, or 10.2 per cent.

This incidence is considerably lower than the generally accepted figure of 30 per cent, but is due no doubt to the fact that there were relatively few cases (16) of moderate vascular disease, and the single case of severe vascular disease required interruption of pregnancy at an early stage.

Incidence of Primary True Toxemia.—

Table III indicates that the incidence of primary true toxemia, 2.3 per cent, was likewise considerably lower than the generally accepted figure of 6

per cent. It will be seen, however, that even though the frequency of both vascular disease and true toxemia was lower than expected, the proportionate reduction was the same in each case. Variations in toxemia rates in different localities are probably related to differences in the frequency and degree of vascular disease. We have included abruptio placentae among the cases of primary and superimposed toxemia, since, by all criteria, clinically and pathologically[2] it conforms to toxemia.

TABLE III. INCIDENCE OF PRIMARY TRUE TOXEMIA IN 1,000 CONSECUTIVE PREGNANCIES FROM SEVEN MONTHS TO TERM, IN PRIVATE PRACTICE

	NUMBER
Pre-eclampsia	
Mild	9
Moderate	9
Severe	1
Abruptio	3
Eclampsia	1
Total	23 or (2.3%)

Hypertension, Antepartum and Residual, in Normal and Vascular Disease Cases.—

Table IV, *A*, indicates that among 859 cases showing normal retinal findings, there was no hypertension early in pregnancy or at term, and at the end of the puerperium only 20 cases or 2.3 per cent showed an elevation of diastolic pressure of 80 to 100 mm. Hg.

Table IV, *B*, indicates that among the mild and moderate cases of vascular disease (106 cases), a normal diastolic blood pressure of less than 80 mm. Hg was found in all early in pregnancy. At term only 9.3 per cent of the patients still had a normal diastolic pressure; in 49.5 per cent it was elevated to 80 to 90; in 35.5 per cent to 90 to 100, and in 5.6 per cent it reached 100 to 110 mm. Hg.

TABLE IV. DIASTOLIC BLOOD PRESSURE AT ONSET OF PREGNANCY, AT TERM AND AT END OF PUERPERIUM

A. In 859 Normal Pregnancies.—

	BLOOD PRESSURE		
	60-80	80-100	100-110
Early pregnancy	859	0	0
Term	859	0	0
End of puerperium	839	20 (2.3%)	0

B. In 107 Pregnancies Complicated by Mild and Moderate Vascular Disease.—

	BLOOD PRESSURE			
	60-80	80-90	90-100	100-110
Early pregnancy	107 (100%)	0	0	0
Term	10 (9.3%)	53 (49.5%)	38 (35.5%)	6 (5.6%)
End of puerperium	78 (72.9%)	13 (12.1%)	12 (11.2%)	4 (3.7%)

At the end of the puerperium, in 72.9 per cent of the cases, the diastolic pressure had returned to normal; in 12.1 per cent it was still elevated to 80 to 90; in 11.2 per cent, 90 to 100, and in 3.7 per cent, 100 to 110 mm. Hg.

This is in marked contrast to the results shown in Table IV, *A*, and indicates that retinal examination may be relied upon to determine whether a rise of blood pressure may be expected in the eighth and ninth months. It also indicates that with a background of vascular disease the blood pressure re-

mains elevated to and beyond the end of the puerperium and lends some support to the belief that pregnancy aggravates vascular disease.

We have further noted that occasionally a patient who shows normal retinal findings early in pregnancy may develop a mild or moderate hypertension, a mild proteinuria, and a clinical behavior in the ninth month which are consistent with mild vascular disease. On retinal examination of such patients near term, it has been of interest to note that during pregnancy, the retinal picture has changed from normal to one of mild vascular disease. This suggests that pregnancy occasionally tends to aggravate a more latent form of vascular disease or possibly to initiate a mild degree of vascular disease.

Hypertension, Antepartum and Residual, in Cases of Superimposed Toxemia.—

That vascular disease tends to be aggravated by superimposed toxemia is shown in Table V in which it is noted that in 5 cases (21.7 per cent) of primary true toxemia there was a diastolic pressure of 80 to 100 mm. of mercury persisting at the end of the puerperium, whereas in 10 cases (54.5 per cent) of superimposed toxemia there was a similar persistence of hypertension. In other words, the tendency to a persisting hypertension was more than twice as great when toxemia was superimposed on a background of vascular disease.

TABLE V. INCIDENCE OF TRUE TOXEMIA (PRIMARY AND SUPERIMPOSED) IN 1,000 CONSECUTIVE PREGNANCIES, SEVEN MONTHS TO TERM, IN PRIVATE PRACTICE

	PRE-ECLAMPSIA			ECLAMPSIA	ABRUPTIO	TOTAL
	MILD	MOD.	SEVERE			
Primary True Toxemia	19			1	3	23
Superimposed Toxemia	8			2	1	11
Total						34 (3.4%)

5 cases primary true toxemia showed diastolic blood pressure of 80-100 at end of puerperium (21.7%).

10 cases superimposed toxemia showed diastolic blood pressure of 80-100 at end of puerperium (54.5%).

Proteinuria in Vascular Disease, Primary True Toxemia, and Superimposed Toxemia Complicating Pregnancy.—

Table VI indicates that in approximately two-thirds of the cases of mild and moderate vascular disease there was no proteinuria in the ninth month when the blood pressure showed the characteristic elevation. Only 2.2 per cent of the cases of mild vascular disease showed as much as a two plus proteinuria, in contrast to 18.7 per cent when the vascular disease was of moderate degree.

This is also in marked contrast to the much greater degree of proteinuria accompanying a similar elevation of blood pressure when due to primary true or superimposed toxemia. A sudden change from a negative or a mild proteinuria of vascular disease to heavy flocculent proteinuria is the most reliable indication that toxemia is becoming superimposed.

Additional indications are found in the sharp superimposed rise in blood pressure and the appearance of localized spasms in the retinal arterioles. It may truly be stated that there is no condition complicating pregnancy which so frequently sets the stage for fulminating abruptio or eclampsia as a moderate or severe degree of vascular disease.

The hypertension of vascular disease is much reduced by complete rest in bed but that of true toxemia is very little if at all benefited and tends to rise still higher. This difference in response to rest serves as a further means of differentiating vascular disease and true toxemia.

TABLE VI. INCIDENCE OF PROTEINURIA IN 107 CASES OF MILD, MODERATE AND SEVERE VASCULAR DISEASE

	MILD		MODERATE		SEVERE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
No proteinuria	60	66.6	10	62.5		
+	28	31.1	3	18.7	1	
++	2	2.2	3	18.7	Pregnancy interrupted at 7 weeks	
Total	90		16		1	

Finally, examination of the formalin-fixed placenta furnishes a most dependable means of determining whether superimposed toxemia was present in any case of vascular disease. Acute infarction of the "E" type[2] is consistently present whenever there is a sudden heavy increase in proteinuria and a superimposed sharp rise in blood pressure, and is usually extensive. It is sometimes the only indication of true toxemia or that the convulsions were eclamptic in origin and not of some other type. The toxemia may have been so fulminating that convulsions occurred without a rise in blood pressure, proteinuria of any significant degree, and without spasms in the retinal arterioles.[3]

Conclusions

1. The practice of obstetrics requires a reliable means of recognizing vascular disease as a complication of pregnancy.

2. Ophthalmoscopic examination, together with a knowledge of the clinical manifestations, furnishes a simple means of recognizing vascular disease and differentiating it from primary true toxemia. A satisfactory degree of proficiency may be developed by making routine retinal examinations early in pregnancy.

3. It is possible to predict in 90 per cent of normotensive cases by retinal examination early in pregnancy that hypertension will develop late in pregnancy.

4. When hypertension of vascular disease develops late in pregnancy, more frequent prenatal observations are necessary on account of the increased danger of acute superimposed toxemia.

5. The more marked the vascular disease, as recognized by increased disturbance in arteriovenous ratio, increased light reflex, and arteriovenous compressions, the earlier the development of hypertension in pregnancy.

6. Residual hypertension at the end of the puerperium is much more frequent among cases complicated by vascular disease and especially among those which developed superimposed toxemia.

7. The occasional change from normal retinal findings early in pregnancy to those of mild vascular disease late in pregnancy suggests that pregnancy may aggravate a more latent form of vascular disease or possibly initiate a mild vascular disease.

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STUDIES ON PREMATURITY

III. THE INFLUENCE OF TOXEMIA OF PREGNANCY ON FATALITY RATE

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IN A study[1] of 794 premature infants delivered as single births at the Jewish Hospital of Brooklyn during the five-year period from 1941 to 1945, it was found that toxemia of pregnancy was the most frequent of all maternal complications. Because our previous report indicated also that toxemia of pregnancy was responsible for the highest incidence of stillbirths it seemed desirable to investigate the possible deleterious effect of this complication on the liveborn infants of such mothers. The present paper, therefore, concerns itself with a comparative analysis of the survival of infants born of toxemic and nontoxemic mothers during the aforementioned period. Only babies born as single births were considered. No distinction was made between preeclamptic and nephritic toxemia. As in our previous investigations, all babies weighing up to 2,250 grams were included in the study and there were no exclusions on the basis of "nonviability."[1, 2]

There has been much speculation as to the effect of severe maternal toxemia on the liveborn premature infant. Breese,[3] in an analysis of 173 cases, is of the opinion that maternal toxemia has no influence on the ultimate survival of the offspring. On the other hand, Taylor and his associates[4] conclude from their studies that infants born of mothers suffering from complications of pregnancy have a mortality rate four or five times as high as those born of normal mothers. Their analysis included 34 cases of toxemia of pregnancy. Diddle and Plass[5] report on 160 infants born alive of mothers with toxemia of pregnancy. An analysis of their data does not reveal any significant difference in the neonatal mortality rate of these babies as compared with those born of nontoxemic mothers.

Material

In the present series, there were 109 babies born alive to mothers who had toxemia of pregnancy. As in our previous reports,[1, 2] these infants were separated according to length of gestation periods into four groups: (a) 29 weeks or less, (b) 30 to 33 weeks, (c) 34 to 37 weeks, and (d) 38 to 40 weeks. The weight categories which were selected were: (a) less than 1,000 grams, (b) 1,000 to 1,499 grams, (c) 1,500 to 1,999 grams, (d) 2,000 to 2,250 grams.

In Table I are recorded the comparative fatalities in relation to the different gestation periods. It will be observed that 9 of the 109 infants born of toxemic mothers died, the over-all fatality rate being 8.3 per cent. This figure may be compared with a fatality rate of 24.8 per cent of 528 infants born of nontoxemic mothers. A detailed study of these two groups, taking into ac-

count the factors of duration of gestation and of birth weight, offered an explanation for the difference in the fatality rates. It will be noted that in the group of toxemic mothers there were only 16 babies born alive after gestation periods of 33 weeks or less, an incidence of 14.6 per cent as compared with 45.6 per cent for infants in the nontoxemic group. Since our earlier study[2] demonstrated the close correlation between length of gestation period and fatality of premature infants it is clear that one must take into account the much higher proportion of infants born after short gestation to nontoxemic mothers. This difference undoubtedly accounts for the seemingly unfavorable over-all fatality in the normal as compared with the toxemic group. Moreover, when the samples were adequate for comparison, the fatality rate was much the same for infants, whether born of toxemic or nontoxemic mothers. Thus, for gestation periods above 34 weeks, fatality rates in all instances varied from 7.5 per cent to 2.9 per cent. In the gestation period of 30 to 33 weeks the difference in percentage fatality between the two groups was 16.4 ± 9.3, a figure which is less than twice its probable error and therefore not statistically significant. The marked difference in percentage of fatality for gestation periods of 29 weeks or less, 33.3 per cent in the toxemic as against 83.7 per cent in the nontoxemic group, must be completely discounted because of the inadequate size of the toxemic group.

TABLE I. NEONATAL FATALITY IN RELATION TO GESTATION PERIOD OF BABIES BORN OF NORMAL AND TOXEMIC MOTHERS

GESTATION PERIOD	BABIES BORN OF MOTHERS WITH TOXEMIA OF PREGNANCY				BABIES BORN OF NONTOXEMIC MOTHERS			
	NUMBER OF CASES	PER CENT OF TOTAL	NUMBER DIED	PER CENT FATALITY	NUMBER OF CASES	PER CENT OF TOTAL	NUMBER DIED	PER CENT FATALITY
29 weeks or less	3	2.7	1	33.3	92	17.4	77	83.7
30-33 weeks	13	11.9	5	38.5*	149	28.2	33	22.1†
34-37 weeks	59	54.1	2	3.4	173	32.8	13	7.5
38-40 weeks	34	31.2	1	2.9	108	20.5	7	6.5
Unclassified					6	1.1	1	16.7
Total	109	99.9	9	8.3	528	100.0	131	24.8

*Probable error = 38.5 ± 9.0.
†Probable error = 22.1 ± 2.3.
Probable error of difference = 16.4 ± 9.3. (This figure indicates lack of statistical significance.)

TABLE II. NEONATAL FATALITY IN RELATION TO BIRTH WEIGHT OF BABIES BORN OF NORMAL AND TOXEMIC MOTHERS

WEIGHT	BABIES BORN OF MOTHERS WITH TOXEMIA OF PREGNANCY				BABIES BORN OF NONTOXEMIC MOTHERS			
	NUMBER OF CASES	PER CENT OF TOTAL	NUMBER DIED	PER CENT FATALITY	NUMBER OF CASES	PER CENT OF TOTAL	NUMBER DIED	PER CENT FATALITY
Less than 1,000 grams	0				54	10.2	53	98.1
1,000-1,499 grams	18	16.5	4	22.2*	61	11.2	32	52.5†
1,500-1,999 grams	52	47.7	4	7.7	178	33.7	30	16.8
2,000-2,250 grams	39	35.8	1	2.6	225	42.6	6	2.7
Unclassified					10	1.9	10	100.0
Total	109	100.0	9	8.3	528	99.6	131	24.8

*Probable error = 22.2 ± 6.5.
†Probable error = 52.5 ± 4.3.
Probable error of difference = 30.3 ± 7.8.

In Table II are listed the comparative fatality rates in relation to different weight categories. The most striking difference to be noted here is that in the weight class of 1,000 to 1,499 grams the percentage fatality of infants of the toxemic group was 22.2 as compared with 52.5 in the nontoxemic group. The difference between these two groups is 30.3 ± 7.8, which is almost certainly statistically significant. The apparently favorable influence on the fetus of maternal toxemia does not stand up under critical examination. As has already been mentioned (Table I), the proportion of babies born to toxemic mothers after gestation periods shorter than 34 weeks is much less than that found in the nontoxemic group. One must therefore conclude that infants with birth weights of 1,000 to 1,499 grams who are born to toxemic mothers are more mature than those of comparative weight born to nontoxemic mothers.

These findings can be further demonstrated by calculating the expected fatality rate after the method described by Breese,[3] using weight class and gestation period as base lines for separate calculation. Briefly this consists of multiplying the number of cases in each weight class or gestation period by the percentage fatality for that weight group or gestation period and dividing the sum of all these by the total number of cases.

The expected fatality rate using the gestation period as a base line was determined as follows:

GESTATION PERIOD	PER CENT FATALITY OF BABIES BORN OF NON-TOXEMIC MOTHERS	TOTAL NUMBER OF BABIES BORN OF TOXEMIC MOTHERS	EXPECTED NUMBER OF DEATHS OF BABIES BORN OF TOXEMIC MOTHERS
Less than 29 weeks	83.7	3	2.51
30 to 33 weeks	22.1	13	2.87
34 to 37 weeks	7.5	59	4.43
37 to 40 weeks	6.5	34	2.21
		109	12.02

12.02 ÷ 109 × 100 = 11.0 per cent—expected fatality rate

The expected fatality rate using the weight class as the base line for calculation was as follows:

WEIGHT GROUP	PER CENT FATALITY OF BABIES BORN OF NON-TOXEMIC MOTHERS	TOTAL NUMBER OF BABIES BORN OF TOXEMIC MOTHERS	EXPECTED NUMBER OF DEATHS OF BABIES BORN OF TOXEMIC MOTHERS
Less than 1,000 grams	98.1	0	0
1,000 to 1,499 grams	52.5	18	9.45
1,500 to 1,999 grams	16.8	52	8.73
2,000 to 2,250 grams	2.7	39	1.05
		109	19.23

19.23 ÷ 109 × 100 = 17.6 per cent—expected fatality rate

The true fatality rate of the babies born of mothers with toxemia of pregnancy was 8.3 per cent, nine out of 109 babies dying. Since the expected fatality rate calculated on the basis of gestation period was 11.0 per cent (probable error of difference = 2.7 ± 2.5), the toxemia of pregnancy exerted no demonstrable effect. On the other hand, the expected fatality rate calculated on the basis of birth weight was 17.6 per cent, a figure which is statistically different from the true fatality rate (probable error of difference = 9.3 ± 2.9).

These differences are a reflection of two accepted obstetrical facts. The first is that toxemia of pregnancy rarely occurs before the thirtieth week of gestation, so that infants born of toxemic mothers almost always weigh more than 1,000 grams (Table II). The second factor is that placental changes in toxemic pregnancies adversely affect growth as indicated by the weight at-

tained by the infant at birth. It would seem from our findings, however, that although weight is affected, the other maturing factors of the infant continue in a normal manner as the gestation progresses.

From Table II it will be seen that the fatality rate of babies born of toxemic mothers in the gestation period of 34 to 37 weeks equalled that of babies born between 37 to 40 weeks. This would indicate that in mothers with toxemia of pregnancy, from the point of view of the chances of survival of the fetus, it would not be necessary to carry pregnancy beyond 34 weeks.

Summary and Conclusions

Of 109 premature infants born alive to mothers who had toxemia of pregnancy, 9 died, giving an over-all fatality rate of 8.3 per cent. This was compared with a fatality rate of 24.8 per cent in a group of 528 premature babies born of mothers who had no toxemia of pregnancy. The difference in the over-all fatality rates was accounted for by the greater proportion of babies born after longer periods of gestation to toxemic mothers. There was no difference in the fatality rates in either group for comparable gestation periods. This conclusion was further substantiated by the demonstration that on the basis of gestation period the expected fatality rate for babies born of toxemic mothers was statistically not different from that of babies born of mothers who had no toxemia of pregnancy.

Data based on a study of the relation of fatality rate to gestation period showed that from the standpoint of the fetus it would not be necessary in toxemic cases to carry pregnancy beyond 34 weeks.

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THE VIABILITY OF THE CAST-OFF MENSTRUAL ENDOMETRIUM

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THE histogenesis of endometriosis is still under discussion, although Sampson's implantation theory has been widely accepted in this country. Some experimental work has been advanced to support Sampson's hypothesis but evidently no one has shown definitely that the endometrium exfoliated at menstruation is capable of survival and growth. The purpose of this communication is to show that under some conditions cast-off menstrual endometrium is viable in tissue culture preparations.

A contraceptive diaphragm was inserted in the vagina on the second day of menstrual bleeding and left in place from eight to twelve hours. After removal the diaphragm was placed in a sterile Petri dish and the collected fluid was immediately examined for bits of tissue. In two out of seven instances sufficient material was obtained for tissue culture explantation.

Materials and Methods

The tissues were cut in pieces about 1 mm. square and transferred to a 50 mm. centrifuge tube. Approximately 15 ml. of Tyrode's solution containing 200 units of penicillin and 2 mg. of streptomycin per milliliter were added and the tube rotated until the tissue was uniformly distributed. The tube was allowed to stand at room temperature for ten minutes until the larger fragments settled, leaving a supernate containing cellular debris and blood cells. The supernate was then removed by suction and the fragments washed again. After three washings the fragments were ready for explantation.

Cultures were made in large hanging drop slides in the following manner: One drop of Tyrode's solution was placed on a square mica coverslip (40 by 40 mm.) and covered with a round coverslip (21 mm.). A drop of reconstituted rooster plasma* was placed on the round coverslip, a small fragment of tissue added, and the drop coagulated by the addition of an equal amount of 20 per cent chick embryo extract and human umbilical cord serum. After the plasma had coagulated, the coverslip was inverted over a depression slide, the chamber sealed with petroleum jelly and paraffin, and the slide placed in the incubator at 37° C.

In the majority of cultures difficulty was experienced with liquefaction of the clot. "Patching" of the lysed area with plasma was so time-consuming and difficult that it was abandoned in favor of Kunitz's soybean trypsin inhibitor.[1] The incorporation of 0.2 ml. of an 0.35 per cent solution of this inhibitor into the medium as suggested by Fischer[2] entirely prevented liquefaction.

Observations

Cultures were examined at 24 hour intervals and were washed in Tyrode's solution and re-fed with equal parts of umbilical cord serum and 20 per cent chick embryo extract every three days.

*Lyophylized rooster plasma obtained commercially from Difco Laboratories, Inc., Detroit, Michigan.

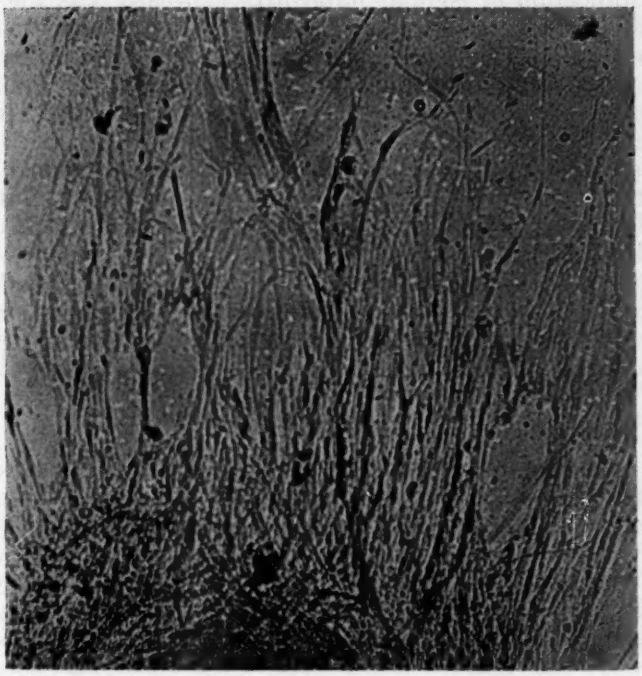

Fig. 1.—Radial growth of fibroblasts. Photographed in the living state.

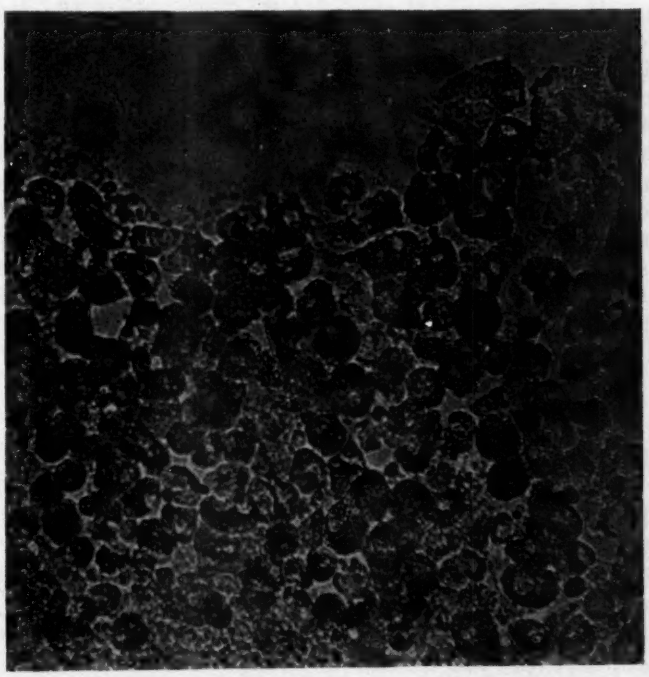

Fig. 2.—Outgrowth of epithelial elements. Photographed in the living state.

The first indication of cellular outgrowth generally was the appearance of fibroblasts in the form of fine threadlike projections at the margin of the explant.

After three to five days' cultivation, the outgrowth was marked and consisted of radially arranged cells, some of which contained mitotic figures. The cells were adherent to one another except at the periphery where individual cells were in evidence (Fig. 1).

Morphologically the cells appeared as either spindle shaped or filamentous and flat and tended to spread out on the coverglass. They contained varying numbers of fat globules and mitochondria and the oval nuclei contained two or more small nucleoli.

In some cultures, sheets of polygonal cells migrated from the tissue explants. These cells contained cytoplasm and relatively large, round, vesicular nuclei. They resembled the typical outgrowth seen in tissue-cultures of epithelium and exhibited no morphologic resemblance to fibroblastic elements (Fig. 2).

Comment

Previous workers have shown that bits of endometrial tissue from rabbits and monkeys transplanted into the peritoneal cavities of the donor animals will grow in the pelvis but not in the remainder of the peritoneal cavity. Cron and Gey[3] have grown endometrium obtained on the second day of bleeding by gentle curettage. Tissue cultures of the fragments showed radial outgrowths of spindle-shaped cells (connective tissue) and sheetlike outgrowths of epithelial cells at the periphery of the explants. A note appended to their paper states "since this report was submitted for publication additional experiments show that the fragments of the epithelium normally found in the menstrual flow and obtained without the use of a dull curette, are visible," but there is no other evidence that they attempted to grow this tissue. This work has frequently been quoted in support of Sampson's theory. However, since the material was obtained by curette, it most probably included some basal endometrium, a fact which mitigates the value as evidence that cast-off endometrium is viable.

It is generally agreed that the basal layer of endometrium does not participate in premenstrual changes and that it is not cast off at menstruation. That being true, the tissue grown in the present experiments must have been from the functional layer, which obviously would be concerned in any transtubal migration into the pelvic peritoneal cavity according to Sampson's theory.

It is interesting that the cells growing out from the explants were definite fibroblasts in some cultures and quite epithelioid in others. The same divergence was noted in cultures of decidual stroma reported by Stein and Stuermer,[4] who offered the thought that the estrogen-progestin ratio in the medium might determine the direction of growth.

Conclusion

Cast-off endometrium obtained from menstrual fluid has been grown in tissue culture using natural (nonsynthetic) medium. The cells in the outgrowths were either fibroblastic or epithelioid in appearance.

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ONE PREGNANCY STERILITY

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AN EXTREMELY difficult patient to handle in sterility practice would seem to be the one who has been pregnant before and who has not been able to conceive again. Since she has become impregnated satisfactorily before, her natural feeling is that she can do so again at her own decision. Her husband, as well, "obviously" is fertile. Should the couple be disappointed, the physician in charge often is criticized unjustly for failure to achieve complete, quick success. This is softened somewhat if the previous pregnancy has been terminated before term or with catastrophe.

Plan of Study.—It was felt that some information might be gained from the scrutiny of 100 consecutive cases whose common factor was one previous pregnancy, whether it ended in spontaneous or traumatic abortion, uncomplicated term delivery, or complicated delivery. These were private patients, selected from consecutive office files, and given a long enough time to become pregnant after work-up started. This length of time was decided arbitrarily as one year. Interestingly enough, primary sterility cases seem far more common, the ratio being about three to one.

Age.—The average age of this group of 100 patients was 31.4 years, the youngest being 18 and the oldest 47 years of age.

Length of Effort to Become Pregnant Before Treatment Was Instituted.—The statement of duration of conscientious effort to achieve impregnation was taken as given by the patient. The average was 29.6 months.

Previous Obstetrical History.—One of the striking things about this phase was the patient's poor recollection and understanding regarding her past reproductive history. Also, there seemed to be no reticence about revealing past traumatic or criminal abortions, nor about past gonorrheal infections. Only 4 had any past gonorrhea, and in these it was prior to the first pregnancy.

Term pregnancies		61
Premature labors		8
Abortions		31
Spontaneous	23	
Traumatic	4	
Tubal abortions	4	
Previous cesarean section (included in term group)		5
Cephalopelvic disproportion	3	
Placenta previa	2	
Curettage following spontaneous abortion		5

Previous Medical (Sterility) Work-Up in Competent Hands.—Only 5 of the entire group had consulted physicians, in only 2 cases specialists in obstetrics, and none had been given special information other than a casual office call. Each of these 5 had had at least one Rubin test, but no other attempt at a work-up.

Plan of Investigation.—These patients were studied in the usually approved fashion by a complete physical examination, blood count, urinalysis, but no sedimentation rate or Rh determination unless indicated by clinical examination

or by clinical history. Routine basal metabolism study was performed. Endometrial biopsy was taken on the first day of menstrual flow. A Rubin test was done arbitrarily at the start of the calculated fertile period. If unsuccessful, this was repeated a month later and if again unsuccessful, then followed by Lipiodol uterotubograms. The patient was instructed in the use of the basal body temperature chart, as well as shown how to calculate her fertile phase as being from 18 through 10 days before the next expected flow. During this time exposure was planned every 48 hours. These patients were given as well daily dosages of thyroid extract empirically, although this was graded by the basal metabolism rate determination to remain within the range of 0 to plus 5, aided by the patient's response. Stilbesterol in 0.5 mg. doses was given orally from the tenth to the twenty-fourth day of the cycle. A friction sperm test was performed shortly after emission and if the count were 50 million or below, the husband was referred to a competent urologist. Any cervical pathologic conditions, vaginitis, retroversion, and the like, were corrected as concurrent office procedures. General dietary and hygienic methods were advised.

Analysis of Demonstrable Defects.—

Tubal occlusion	57
Hypothyroidism	2
Failures of habitual ovulation	6
Male defects	19
Psychosomatic or functional causes	2

Results.—

Failed to persist in treatment (under one year)		58
Successes		11
Term infants	7	
Spontaneous abortion	4	
Failures (advised to adopt after work-up had been completed)		9
Still under treatment (duration one year or over)		22

Comment

Consideration of the above figures in a small group of private patients would suggest that the single greatest cause of failure to conceive was impatience rather than mechanical impediment. True, some of these patients may have continued treatment under another physician's care and cannot be calculated in the series. However, in those who did persist, 11 of 42 patients achieved pregnancy although 4 of these did not carry to viability. It would seem then that the physician's greatest problem is to give the couple an understanding of the problem and enlist their cooperation in giving an adequate period of time to necessary correction and maintenance of all factors known to be important in successful impregnation. This has long been recognized but it has led to the feeling in this office that this is our single most potent therapeutic weapon.

The second greatest cause of infertility would seem to be tubal occlusion. One can only speculate on the causes of this finding, and we do not wish to enter into the discussion of the value of the various tests to differentiate between false occlusion due to spasm and organic occlusion. Of this group of patients, 61 had had term pregnancies without known complications although there were 5 cesarean sections. Eight had had premature labors. Thirty-one had had abortions, although only 4 had been criminally induced and none of the patients had required hospitalization subsequently. Four had had tubal abortions, on inquiry, which would suggest an abnormally high incidence of disorder of downward migration of the fertilized ovum. Five also had had curettage after

spontaneous abortion, which might indicate retention of products to a point where intervention was necessary because of hemorrhage or infection. Gonorrhea had been present by history in only 4 cases.

The incidence of 2 cases of placenta previa would suggest some abnormality of nidation mechanism as would the unusually high percentage of spontaneous abortion in the successfully treated group (4 of 11 pregnancies).

Conclusions

It would seem that there must be some agent other than infection operative in these cases of women who were once pregnant. We all agree that unrecognized infections presumably by low-grade pathogens or saprophytes may complicate abortion, miscarriage, or term delivery. These patients had no present knowledge of such complications. Also, the asymptomatic cervical erosion may play some part in subsequent inflammatory tubal occlusion. Certainly, there is clinical impression that such may be the case.

A reasonable explanation for the high incidence of tubal occlusion (and the high degree of success in treatment by simple insufflation methods) might be that shedding of the tubal epithelium may stop short of complete extrusion of this detritus each month. "Tubal menstruation" is a somewhat doubtful term, but the cyclic changes in tubal epithelium are well known. Since the majority of these patients are in the older age group—reproductively speaking—it would suggest that this process has been operative for a longer period of time. The sterility expert may be likened to the plumber who clears a partially or completely plugged line with his gear. Certainly, we all are at a loss to explain the not infrequent success attendant upon a partially successful gas insufflation in a patient who has been trying unsuccessfully for years to become pregnant. This concept has been borne out at the operating table where no outward evidence of infection past or present is found, yet flushing out of the tubes with saline or clearing by manipulation gives pregnancy. It is interesting to speculate. No discussion need be given to gonorrhea or postabortal infection as obvious agents in occlusion, although neither factor seemed of reasonable significance in this study.

Some suggestions have emerged from preliminary consideration of this group before they were studied statistically. Already suggested has been the imperative need for an adequate education of the couple for a follow-through. If enough time is given to correcting the various abnormal factors (if needed), and to keeping all parts in working order, and the morale high, the single most potent therapeutic agent has been used.

More and more investigators are suggesting the routine use of curettage in all cases of spontaneous abortion even though the observer may feel that the abortion has been complete. Certainly this is a procedure of ease and safety. Infection in retained products may play some part in subsequent sterility as suggested by the frequency of its appearance in this group of patients.

There should be wider use of "therapeutic" dosages of sulfonamides and/or the antibiotics in any patient showing a morbid reaction, whether there be clinical symptoms or not.

707 Broadway

LIBERATION OF BETA-GLUCURONIDASE ACTIVITY BY BACTERIA CULTURED FROM THE HUMAN VAGINA AND CERVIX*

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CURRENT studies on the activity of the enzyme, β-glucuronidase, were carried out because of observations made in a report by Odell and others.[1, 2, 3] It was reported that the activity of β-glucuronidase in vaginal secretions from women with untreated cervical cancer exceeded 300 gamma of phenolphthalein per milliliter of vaginal secretion per hour of incubation. In addition, it was reported that 20 per cent of women without clinical or cytological evidence of cervical cancer had similar high values in the vaginal secretions, particularly if they were pregnant or if they had evidence of a vaginitis associated with the presence of *Trichomonas vaginalis*. This led to an investigation of the possible role of the bacterial flora of the normal and abnormal vagina and cervix in the liberation of the enzyme, β-glucuronidase.

Material and Method

For this study cervical and vaginal cultures were made from obstetric and gynecologic patients on their routine visits to the University of Chicago Clinics. Among them were cases of histologically proved cervical cancer. Other patients without evidence of genital cancer had normal and infected vaginas. The culture material was plated on a blood agar medium and incubated aerobically and anaerobically. The method of isolating bacteria on blood agar gave as complete a selection of organisms as was deemed practical. The following organisms were isolated: Diptheroids, Alpha Streptococci, *Staphylococcus aureus, Bacillus cereus, Bacillus aerogenes, Escherichia coli,* and *Bacillus subtilis.* Pure cultures of each of these organisms were cultivated and studied on three media: proteose peptone broth, dextrose brain broth (Difco), and a medium described by Beuhler and Doisy.[4] The latter medium contained 1 per cent proteose peptone, 0.3 per cent beef extract, and 0.5 per cent sodium chloride. Enough menthol glucuronide to make a 0.7 per cent solution was added to an equal number of tubes containing the medium described by Beuhler and Doisy. Trichomonads (free from bacteria)† were grown in a medium described by Kupferberg and co-workers.[5] The medium volume was standardized at 10 ml. Bacteria were counted by a method described by Greene and Hesseltine.[6] Enzyme activity was measured colormetrically.[7] Units of activity are expressed as the γ of phenolphthalein liberated per milliliter of medium per hour of incubation. All tests were made in duplicate. Suspensions of the bacteria in the medium as well as the supernatant fluid following centrifugation were tested separately.

*This study was supported in part by the Cancer Research Fund of the Chicago Lying-in Hospital and by an Institutional Grant from the American Cancer Society.

†*Trichomonas vaginalis* cultures were obtained by courtesy of the Ortho Research Foundation, Raritan, New Jersey.

Results

Bacteria grown in proteose peptone and brain broth (Difco) showed no activity of β-glucuronidase after 2, 3, 4, 5, 7, 16, and 35 days. Bacteria grown in the medium described by Beuhler and Doisy[4] likewise showed no activity. However, the addition of menthol glucuronide to the latter medium resulted in a significant liberation of β-glucuronidase activity by all of the bacteria studied. The day of growth upon which the maximum activity was observed varied among and within the various strains studied. The maximum activity liberated by the seven strains on five different occasions ranged from 6 to 290 units. The greatest activity occurred with *E. coli*, the least with Diptheroids. Both bacterial suspensions and bacteria-free supernatant media exhibited enzyme activity (Table I).

TABLE I. STRAINS OF BACTERIA CULTURED WITH 0.7 PER CENT MENTHOL GLUCURONIDE

	UNITS OF ACTIVITY* IN BACTERIAL SUSPENSIONS			
ORGANISM	DAY OF GROWTH 1	DAY OF GROWTH 2	DAY OF GROWTH 5	DAY OF GROWTH 16
B. cereus	4	4	10	1
Diptheroids	4	4	4	1
B. subtilis	4	13	1	0
Staph. aureus	4	2	3	1
Alpha strep.	4	5	1	6
E. coli	290	208	45	10
B. aerogenes	6	34	2	1

*Units of activity are expressed as the average of duplicate cultures and tests in γ of phenolphthalein liberated/ml. of media/hour of incubation.

The bacteria-free supernatant of the medium exhibited as much activity as the bacterial suspension.

Bacteria-free cultures of *Trichomonas vaginalis* produced an average of 12 γ/ml. of medium/hour of incubation after 23 days' growth on media without menthol glucuronide. The addition of menthol glucuronide to the culture medium increased activity to an average of 20 γ after 23 days of growth. Alpha Streptococci added to a bacteria-free culture of *Trichomonas vaginalis* grown in medium with menthol glucuronide increased the activity of β-glucuronidase significantly—an average of 32 γ. Furthermore, cultures of *Trichomonas vaginalis* with mixed bacteria obtained from clinic patients were found to be greater in β-glucuronidase activity than bacteria-free cultures of *Trichomonas vaginalis* (Table II).

TABLE II. TRICHOMONAS VAGINALIS AND ALPHA STREPTOCOCCUS

	UNITS OF ACTIVITY* AFTER 23 DAYS OF GROWTH		
SAMPLES	A†	B†	C†
1	1	21	45
2	1	21	34
3	1	19	4
4	1	19	27

*Units of activity are expressed as the averages from duplicate cultures and tests in γ of phenolpthalein liberated/ml. of medium/hour of incubation.

†A, Culture of Trichomonas in Kupferberg's medium.

B, Culture of Trichomonas in Kupferberg's medium with 0.7 per cent menthol glucuronide.

C, Mixed culture of Trichomonas and Alpha Streptococci in Kupferberg's medium with 0.7 per cent menthol glucuronide.

Bacterial counts performed on stock cultures of *E. coli* grown in the medium described by Beuhler and Doisy[4] with menthol glucuronide show that

the liberation of enzyme is closely associated with the initial growth phase of the bacteria (Table III).

TABLE III. E. COLI AND BACTERIAL COUNT*

SAMPLES		HOURS OF INCUBATION				
		8	24	48	72	96
I	Mil.†	2.00	3.60	4.56	3.76	3.68
	Gl.†	0.9	10.7	1.3	1.7	1.7
II	Mil.	1.60	3.20	4.64	3.20	3.36
	Gl.	0.8	11.9	1.7	2.0	2.0
III	Mil.	1.56	3.50	4.80	4.60	4.80
	Gl.	1.0	11.3	4.7	2.4	2.1

*The bacterial control (bacteria + medium but without menthol glucuronide) read 0.3 units.

The stock cultures of *E. coli* used in this experiment failed to liberate as much enzyme as the coli isolated from a human source.

†Mil.—Express the bacterial count in millions/ml. of medium.

Gl.—Figures express average of duplicate cultures and tests in γ of phenolphthalein liberated/ml. of medium/hour of incubation.

Comment

The results of this study confirm the findings of Beuhler and Doisy[4] who observed the liberation of β-glucuronidase activity by *E. coli* cultured in medium containing menthol glucuronide. The study lends evidence that at least part of the activity present in the vaginal secretions of women with and without cervical cancer could be the result of bacterial action. This would assume that other glucuronides of human origin were responsible for the metabolic adjustment that bacteria will apparently make to their cultural environment.

The association between the initial increase in number of bacteria and the liberation of enzyme ally this enzyme with the process of growth. It is of interest that others[7] have found an increased activity of β-glucuronidase in association with cellular proliferation in animal tissues. In addition, a synergistic action between bacterial flora and *Trichomonas vaginalis* in respect to the liberation of the enzyme seems likely since the activity was more in mixed cultures.

Summary

In the presence of menthol glucuronide each of seven different bacterial strains isolated from the normal and abnormal vagina and cervix of human beings liberated the enzyme, β-glucuronidase. Cultures of *Trichomonas vaginalis* with bacteria liberated more enzyme activity than bacteria-free cultures of *Trichomonas vaginalis*.

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Department of Case Reports New Instruments, Etc.

ECLAMPSIA WITHOUT CONVULSIONS COMPLICATED BY ASCITES WITH RECOVERY

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SINCE King[3] brought the literature up to date in 1933 (44 cases including his), only two more cases have been added to date to the literature. One of these was reported in 1944 by Reis and Bernick.[4] The other is mentioned in Dieckmann's book, *Toxemia of Pregnancy.*[1] We have been able to locate one similar case, in a report entitled "Ascites in Pregnancy," by Golden,[2] who states that as far as he can ascertain in a review of the literature, pregnancy and ascites are mentioned in the literature thirty-eight times. Only eleven of these cases are reported in English and the last mention was made in 1887.

Mrs. L. H. (13734), aged 38 years, gravida ii, para i, was admitted to St. Joseph Hospital on Sept. 26, 1949.

Past history: She had had cystitis and pyelitis in 1940. Normal delivery by low forceps and episiotomy of a normal female child occurred in May, 1941, the antepartum and postpartum course being entirely normal. The patient developed extrasystoles in early 1949. Examination by a cardiologist revealed no abnormalities of the heart. The patient did have measles on April 8, 1949, at which time she was approximately five weeks pregnant. No operations or any serious illness were reported.

Last menstrual period was Feb. 15, 1949, and the expected date of confinement Nov. 22, 1949. Initial physical examination on April 22, 1949, was negative. The pregnancy progressed normally and on Sept. 13, 1949 (the last office visit), the blood pressure was 110/60, pulse 84, no extrasystoles, urinalysis normal, weight 141 pounds, a gain of 9 pounds, and hematocrit of 3.8. A 29 weeks' gestation examination showed a cephalic presentation, in an ROA. However, it was remarked at the time that the uterus was perhaps small for that period of gestation.

On admission to the hospital the patient complained of severe intense headache and backache of four days' duration. This backache first began after the patient had worked in her flower bed, beginning first as severe low back pain then radiating up the spine to the head and neck. This pain later seemed to be more intense over the liver area posteriorly. The next day after the onset of backache she noticed the abdomen beginning to enlarge very, very rapidly. Epigastric pain, blind spells, dizziness, and edema of the feet, ankles, hands, and face then occurred. The abdomen continued to enlarge rapidly and she became very uncomfortable from abdominal pressure.

Physical examination on admission revealed a well-nourished white woman not appearing acutely ill. Blood pressure 170/110, pulse 72, respiration 24, temperature 98.6° F., weight 154 pounds (a gain of 13 pounds in 13 days). Slight edema of the face was noted. The abdomen was greatly enlarged, out of proportion to the period of gestation. The uterus could not be outlined definitely by abdominal palpation, but by pelvic examination the fundus

could be felt at the level of the umbilicus. The uterus seemed to be smaller than at the office examination, two weeks previously. A fluid wave with shifting dullness was present. No fetal heart tone or movements could be noted. Roentgenographic examination of the abdomen confirmed the diagnosis of ascites. The extremities showed mild edema of the feet and ankles.

Laboratory data: Red blood count 4,560,000; hemoglobin 12.3 Gm., white blood count 7,950 (polymorphonuclear leucocytes 79 per cent), serum protein 5.95 Gm./100 c.c., albumin-globulin ratio 1.3:1, chlorides 500 mg./100 c.c. Urinalysis showed 4 plus albumin with 8 to 10 white blood cells per high power field.

On Sept. 29, 1949, the icteric index was 11 units. Examination of the ascitic fluid on Sept. 29, 1949, revealed a clear straw-colored fluid, specific gravity 1,008, no bacteria found, no evidence of malignant cells, and cultures were negative.

The patient was given 500 c.c. of 20 per cent glucose in distilled water every 8 hours intravenously, 2 c.c. of 50 per cent magnesium sulfate intramuscularly every 6 hours, luminal sodium, grains 2, intramuscularly every 8 hours. Magnesium sulfate, one ounce by the mouth, was continued each morning, with a milk and fruit juice diet. Five hundred c.c. pooled plasma were given intravenously on Sept. 29, 1949. No clinical improvement was noted during the next four days. The blood pressure continued to stay elevated. The urine albumin continued 4 plus, but with a satisfactory output. Weight gain of 1½ pounds occurred. Edema of the extremities and face cleared, but the abdomen continued to increase in size with distress becoming very acute from pressure. Constant backache and headache with blurring of vision were present. Faint icterus appeared.

Obstetric and medical consultants agreed a paracentesis should be done to relieve the patient's distress and to obtain a specimen of the fluid. A paracentesis was then done just below the level of the umbilicus. Two thousand seven hundred c.c., of a clear straw-colored fluid were obtained. A large amount of fluid could not be removed because of the height of the uterine fundus. After removal of the fluid the fetal heart could be heard very easily with active fetal movements being felt. The patient was relieved completely of the backache and headache.

The next twelve hours after the paracentesis the patient felt very well but then the abdomen began to fill very rapidly again with a recurrence of the severe backache. The patient also became dyspenic. A roentgenogram of the chest revealed pneumonia of the left lower lobe with a small pleural effusion. During the night prior to surgery the site of the paracentesis opened and a large amount of the fluid drained out on the dressing and bed clothes, but at surgery the abdomen was still very tightly distended.

With the patient's condition becoming more and more grave, especially with the rapid recurrence of the ascites and the appearance of hydrothorax and pneumonia, it was felt that the only course of treatment left was immediate termination of the pregnancy, to be followed by abdominapelvic exploration for diagnosis.

On Oct. 1, 1949 (fifth day after admission), under ethylene and cyclopropane anesthesia a classical cesarean section was done through a long right rectus incision. The delivery of a normal living premature male child who cried vigorously, after intertracheal intubation, was done without difficulty. After completion of the cesarean section, with the consultation of a general surgeon, a complete abdominapelvic exploration was done. The findings were entirely negative with the exception of those in the liver. The liver was normal in size and consistency and contained numerous subcapsular hemorrhages over its entire surface. These hemorrhages were not confluent, but ranged from 1 mm. to about 1 cm. in diameter and ranged in color from bright red to almost black. A wedge biopsy was taken from the liver edge.

Pathological examination of the liver tissue and placenta revealed subcapsular hemorrhages of the liver with marked degenerative changes occurring in the liver cord cells. Infarcts of the placenta were present.

Final diagnosis: (1) Toxipathic hepatitis, (2) infarcts of placenta.

Postoperative course: Relatively uneventful. Penicillin and streptomycetin were given. Five hundred c.c. of whole blood and 500 c.c. plasma were given intravenously. The chest

was clear by the fifth postoperative day. No recurrence of any ascites could be determined. The blood pressure gradually dropped with the albumin clearing until at time of discharge on the eleventh postoperative day the blood pressure was 110/78 and there was a faint trace of albumin.

The fetus which weighed at birth only 2 pounds, 7 ounces, expired three days postoperatively.

Six weeks postoperative check revealed weight 130½ pounds, blood pressure 120/50, urinalysis normal. The abdominal incision was healed solid and the pelvic examination was normal.

Slight dimness of vision was still present. The patient still felt weak, but was gradually regaining strength.

We feel that in this we have had one of the most unusual cases ever reported in this category, especially in that paracentesis and the termination of the pregnancy led to the immediate recovery of an otherwise dying patient. We also feel especially fortunate in having the opportunity to see such a liver in a living patient and to obtain a biopsy to support the diagnosis.

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SARCOMA OF THE CERVIX UTERI

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WE FEEL that this case of sarcoma of the cervix is of general interest because of (1) the rarity of the condition; (2) the unusual location of the tumor; and (3) the apparen excellent results obtained by treatment so far in this case.

The chief complaint of the patient, Mrs. G. F., was irregular menses with severe dysmenorrhea for four months. Her menses had been regular every 28 days with 5 days' flow until the last 4 months, when they had occurred every 14 to 21 days with a 7 days' flow. This change in regularity was also accompanied by the development of very severe pain throughout the menses with the passage of clots. The pain being so severe as to necessitate "shots" and complete bed rest. The last menstrual period was Nov. 17, 1947. There was no pelvic pain otherwise, but a thin vaginal discharge occurred at times.

Past history: The patient had been married 8 years ago. She had had no operations or illnesses. She was gravida iii, para iii, oldest child 6 years old, the youngest 14 months. All deliveries were normal.

Physical examination: On Dec. 8, 1947, examination showed a well-developed and well-nourished white woman, 31 years of age, weighing 124 pounds. Blood pressure was 100/60, pulse 84. General physical examination was essentially negative.

Pelvic examination was essentially negative except for a cervix with old bilateral lacerations with a dirty grayish, granular, friable mass about the size of a quarter on the anterior lip. This lesion bled easily and did not involve the anterior or lateral fornices and seemed to be limited entirely to the anterior lip of the cervix.

First procedure: The day after initial examination, at the Methodist Hospital, the cervical lesion was first biopsied and then removed as completely as possible with electrocautery. Frozen section of the biopsy tissue was reported as high grade carcinoma, probably epidermoid. Thirty mg. of radium were then inserted in the cervical canal and ten 2 mg. radium needles were inserted into the cervical tissues around the periphery of the cervix. Five Gm. of sulfanilamide were placed in the vagina and the vagina packed with gauze. A Foley catheter was placed in the bladder. The radium was removed after a dose of 5,000 mg. hr. had been given. The patient was discharged on Dec. 14, 1947, to return on Dec. 31, 1947, for readmission and surgery.

Microscopic sections revealed the lesion to be unquestionably a leiomyosarcoma (Figs. 1 and 2).

Second procedure: The patient was readmitted on Dec. 31, 1947. X-ray of the chest and abdomen on Dec. 31, 1947, revealed no evidence of metastasis. Speculum examination of the cervix the day prior to surgery revealed no trace of the original lesion.

On Jan. 3, 1948, under general anesthesia, a total hysterectomy, bilateral salpingo-oophorectomy with fairly wide excision of the left lateral vaginal fornix and prophylactic appendectomy were done. At the time of operation none of the original lesions could be found and only a small amount of induration and fibrosis in the left lateral fornix was noted.

Careful examination of the surgical specimen revealed no residual tumor. Only radiation reaction of the cervix was found.

The postoperative course was uneventful and the patient was discharged home on Jan. 13, 1948. No medication was given at home.

Fig. 1.

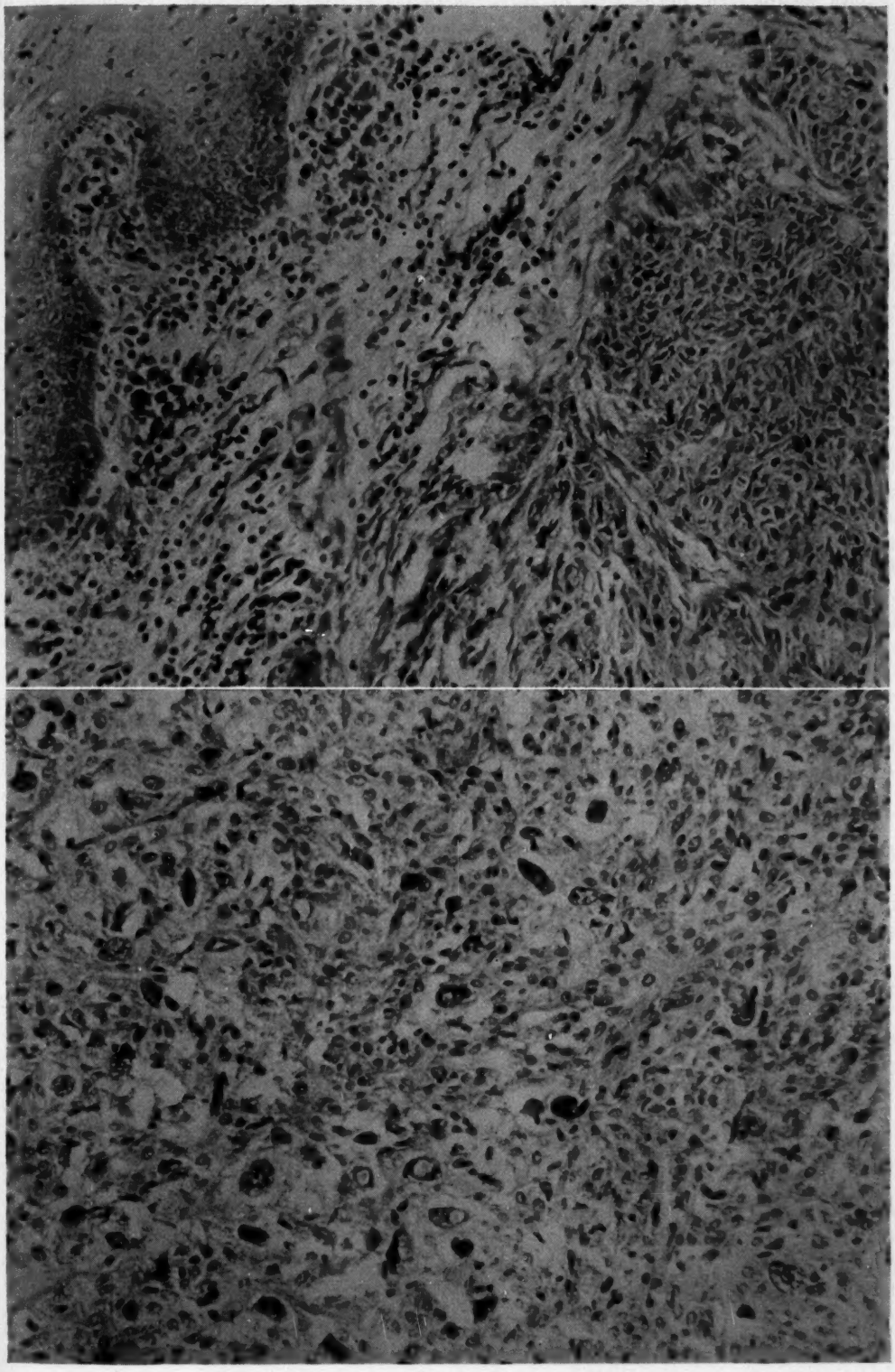

Fig. 2.

Follow-up: The patient has been seen at frequent intervals since treatment. She has gained weight from 109 at time of operation to 121 at time of last visit. Vasomotor symptoms for 12 weeks postoperatively were controlled by 10 mg. of methyl testosterone daily. Since that time, however, she has not taken any medication whatsoever. At no time since treatment has there been any evidence of a recurrence or metastasis.

Comment: Two years is not a criterion of cure, but as sarcoma is usually so rapidly progressive and is not radiosensitive, it is believed that this report should be added to the literature.

ABDOMINAL PREGNANCY WITH A LIVING BABY DELIVERED NEAR TERM*

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THIS is the first abdominal pregnancy in 17,173 deliveries on the maternity service of the French Hospital in New York.

Mrs. R. Z., a white woman, aged 40 years, gravida v, para 0, had her last menstrual period on Dec. 1, 1947, and the estimated date of confinement was Sept. 8, 1948.

Her family history was noncontributory. Her personal history included a tonsillectomy at age 15 years, cystitis on two occasions.

Her menses began at age 16, but were not regular until age 21 years, when they followed a pattern of 28 to 31 days and lasted three days.

When the patient was first seen in May, 1944, she gave a history of having had three miscarriages at two to three months (1934, 1942, and 1943). Physical examination revealed a uterus enlarged to the size of about 8 to 10 weeks' gestation due to a fibromyoma on the right cornu. Her menses were profuse and she had a secondary anemia. This was considered a contributory cause of abortion, but as her basal metabolism was found to be minus 19 per cent, she was placed on thyroid and antianemia therapy. She conceived in November, 1944, but had a spontaneous abortion in January, 1945. A curettage was done for retained secundines, and the fibromyoma on the right cornu was somewhat larger and found to encroach upon the endometrial cavity. Myomectomy was discussed but the patient was reluctant to undergo surgery which would not guarantee a pregnancy. Her metabolism remained low and thyroid therapy was continued.

As her menses became more profuse and occurred at intervals of 25 to 26 days, and clots were passed, a laparotomy was done in August, 1946, and a fibromyoma about 7 cm. in diameter was removed from the posterior wall of the uterus, and several smaller subserous fibromas from the anterior wall. When the large intramural fibromyoma was removed, the endometrium was invaded, but the uterus was reconstructed and the patient made an uneventful recovery.

Following the operation the patient has monthly episodes of staining for one or two days, but no cramps. The uterus was small in size and a uterine sound was passed to a depth of 6 cm. In 1947 the basal metabolism readings were improved and less thyroid was required to keep her in balance. A temperature chart indicated that she was ovulating, but the menses consisted of only a day of spotting. Adoption of a child was discussed and considered. However, in February, 1948, she came to the office with a history of having had her last menses Dec. 1, 1947, and a positive report of an Aschheim-Zondek test done on Jan. 23, 1948. She had some nausea, there were breast changes, and the uterus was enlarged to the size of about 8 weeks' gestation with enlargement on the left cornu. Her thyroid medication was continued and she was also given vitamin E, 25 mg. daily. She had a pink show on January 1, and spotted on March 4, but experienced no cramps. On March 12, the uterus was enlarged to the size of 3 months' gestation and seemed to be regular.

Her progress was uneventful until she was about five months pregnant when she was seen at her home on April 26, 1948, because of severe upper right quadrant pain, which was referred to the shoulder. This had followed overindulgence in ice cream, and was attributed to possible gall bladder disease. With elimination of fats from her diet and administration of saline cathartics she recovered promptly.

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The patient felt life on April 25, 1948, about the twenty-first week, and the fetal heartbeat was heard easily in the lower left quadrant on April 30, 1948.

The pregnancy progressed normally, her weight gain was from 118 to 140 pounds, her blood pressure remained normal for her 98/60 to 116/70. In July the position of the baby was noted to be a breech, right sacrum anterior, but no effort was made to alter this as a cesarean operation had been decided upon for delivery because of the age of the patient and the findings at time of myomectomy. The uterus seemed harder and somewhat irregular on the lower left side which was interpreted as enlargement of an intramural fibromyoma.

The patient was Rh positive, blood group 0, Wassermann negative, and except for a secondary anemia of mild degree her progress was satisfactory.

She was seen at the office on Aug. 13, 1948, at which time she said she had experienced further pain in the upper right quadrant the previous night, and pain in the shoulder similar to the episode in April. Three days later her husband telephoned at midnight saying his wife had had another episode of pain in the upper right quadrant, which had been so severe it had caused her to break out in a sweat, and there was more generalized pain in the abdomen. She was sent to the French Hospital where she was admitted on Aug. 16, 1948, between 1 and 2 A.M., three weeks before the estimated date of confinement.

On admission the patient was very apprehensive, with pain in the upper right quadrant referred to the shoulder, and irregular pain in the abdomen related to the movement of the baby. Her blood pressure was 100/60, pulse 72, respirations 18. The baby was presenting as a breech, and the fetal heartbeat was regular, 140, and heard best at the umbilicus. Her pulse increased in rate in the next hour but the blood pressure improved. A rupture of the uterus was suspected and laparotomy was decided upon. A transfusion of whole blood was started and the abdomen was opened through a suprapubic paramedian incision. Free bloody fluid and old blood clots were found. The infant was lying free in the upper abdomen with the membranes ruptured. A baby boy weighing 5 pounds, 9 ounces, was delivered with no difficulty; he cried at once. After fluid and blood clots were removed and a more careful inspection was made, the placenta was found attached to the omentum and to the fundus of the uterus. The tubes and ovaries were visualized and appeared normal. There was one area on the placenta which was bleeding, this was controlled with a figure of eight suture. The umbilical cord was ligated with chromic catgut and excised close to its attachment to the placenta which was left in situ. The abdomen was closed in layers without drainage. The operation required about 35 minutes and the patient was returned to her room in good condition.

She was given 300,000 units of penicillin daily for five days, her temperature varied from 100 to 101.6° F. the first three days, but was normal thereafter. There remained a nontender mass in the lower abdomen extending to the level of the umbilicus which was present on the eleventh postoperative day, when the mother and baby went home in good condition. The baby was given an evaporated milk formula and weighed 5 pounds, 8 ounces on discharge. The mother's breasts never became engorged at any time after delivery.

About two weeks after leaving the hospital the patient experienced malaise and lower abdominal pain. She had been told the mass was the afterbirth, but its presence was a source of anxiety to her. About twelve weeks after her operation, following some heavy lifting, she experienced severe lower abdominal pain, she had some diarrhea, and had a slight elevation of temperature, she felt cold and clammy, and was readmitted to the hospital on Nov. 5, 1948. Her blood pressure was 108/60, pulse 80, temperature 98.2° F. The abdomen was soft, but there was a tender mass in the left lower quadrant which extended to the level of the umbilicus. The uterus was not clearly outlined on pelvic examination but seemed to be posterior to the abdominal mass. There was some dark vaginal discharge which had continued since delivery. The temperature fluctuated from 98.2° to 103° F. The urine showed 3 plus albumin with clumps of white blood cells, but

this cleared with chemotherapy. Blood counts showed 4,080,000 red blood cells with 12.0 Gm. of hemoglobin, 9,500 white blood cells with 72 per cent polymorphonuclear leucocytes. The sedimentation rate was 28 mm. in 45 minutes.

An x-ray of the lower abdomen showed a diffuse increased density over the pelvic area with compression of the medial side of the sigmoid. There was no calcification and no definitely outlined tumor mass identified. The patient was discharged from the hospital at the end of a week with a normal temperature and her general condition improved.

During the next two weeks at home she experienced slight fever, had cold sweats at night, weakness and spotting of dark bloody vaginal discharge. She lost 16 pounds weight and had more pain in the lower left quadrant. She was readmitted to the hospital on Dec. 6, 1948, about 4 months after delivery.

The mass was still present in the lower abdomen extending to the umbilicus. On pelvic examination the uterus seemed incorporated in the mass which was not very tender, there was no parametritis.

She had 4,260,000 red blood cells, 11.2 Gm. hemoglobin, 20,000 white blood cells with 77 per cent polymorphonuclear leucocytes. The sedimentation rate was 30 mm. in 45 min. The urine showed clumps of white blood cells. A culture of the urine showed hemolytic *Staphylococcus aureus*. A culture from the cervical discharge showed the same organism and also nonhemolytic streptococcus. Blood culture was negative after 48 hours. An Aschheim-Zondek test was negative. Laboratory studies showed that the organism was very sensitive to penicillin, and less so to streptomycin and aureomycin. Therefore she was given massive doses of sodium penicillin, every three hours and Crysticillin, 300,000 units daily, a total of 3.9 million units in all. Her temperature gradually subsided from 103° F. to normal in two weeks' time. The abdominal mass became smaller and nonsensitive, but did not disappear. The patient was allowed home after 17 days in the hospital, on Dec. 23, 1948.

Penicillin was continued at home for two weeks, the abdominal mass decreased in size to about three months' gestation, was more discrete, movable, and nontender. In February, 1949, the uterus was anterior, normal size, freely movable, and the adnexa were negative, no other pelvic mass was palpable. She had her first menstrual period Feb. 22, 1949. This recurred at intervals of every 28 days, scant in amount but lasted three days. In the past few months the amount has decreased and lasts about one day, the interval is every 27 to 28 days. Her metabolism is still below normal and she takes a small amount of thyroid daily but feels well and talks about having another baby. The child developed normally physically and mentally.

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OIL EMBOLISM DURING HYSTEROSALPINGOGRAPHY

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HYSTEROSALPINGOGRAPHY is usually done with little or no misgivings as to the possibility of accidental injection of the iodized oil into the venous plexus of the uterus and uterine vessels. Yet this is said to occur in from 0.4 to 1.8 per cent of such procedures according to several large series of cases reported. The only fatality reported was recorded by Gajzago[1] in 1941.

Many reasons for oil or fat embolism, have been advanced and the most likely causative factors are: direct trauma from the cannula; injection at excessively high pressure; injection when the endometrium is physiologically deficient, as during menstruation and during the first six to eight days after the cessation of the period; injection when the endometrium and cervix uteri have recently been subjected to surgical trauma and unusual permeability of the endometrial tissue.

It is generally agreed that the proper technique is the fractional method of injecting repeated small (2 c.c.) amounts of oil. While in most of the cases reported, a single large dose of 8 to 10 c.c. was used, occasionally accidental intravasation of oil occurs even where the fractional method is used as evidenced by the case we are about to report.

Mrs. R. F., white, aged 29 years, was referred to one of us (N. K.) by Dr. S. G. because of involuntary primary infertility of 3 years' duration. Vaginal examination done on Nov. 7, 1949, showed a nulliparous introitus, slight cervical circumoral erosion, and a uterus normal in size, shape, and position. There was some slight thickening and tenderness in both adnexal regions.

A hysterosalpingography was done in Dr. R.'s office by the fractional method. Two c.c. of Iodochlorol were injected, with x-ray exposure and visualization of the plate before a subsequent 2 c.c. portion was again injected. The right tube was not visualized even after the injection of 6 c.c. of dye. Since a considerable portion of the oil had leaked back into the vagina, a 5 c.c. portion of Iodochlorol and/or Lipiodol was injected under possibly increased pressure in an attempt either to fill the right tube or force it open. While the roentgenogram was being taken the patient complained of slight nausea and faintness. The developed x-ray film showed that the dye had entered the uterine plexus and left uterine vein along with spilling into the peritoneal cavity (Fig. 1).

Realization as to what had happened elicited concern and caution. The patient was not permitted to get off the x-ray table. An ambulance was called and she was immediately removed to Middlesex General Hospital. She was placed in bed with a minimum of handling.

Her general condition was excellent and her complaints minimal. Careful examination failed to reveal any untoward findings. It was decided to keep her in bed for several days notwithstanding the negative findings.

For the first few days of her hospital stay nothing unusual happened. On Nov. 11, 1949, 5 days after admission, the patient began to complain of pain in the lower right chest. She thought this was the result of a cold. Her temperature rose to 101° F. Because of this pulmonary complication an internist (W. S.) was asked to see her in consultation and to take over.

Patient now appeared moderately acutely ill. She complained of mild lancinating pain over the lower axillary region of the right chest which was definitely associated with respiration and cough and intensified by either. She felt flushed and feverish, was perspiring but not chilled. The temperature was 101° F., respirations 20, pulse rate 100 with regular sinus rhythm, blood pressure 125/75. Heart sounds were of good quality with no murmurs present. The breath sounds on the right side at the posterior base were diminished and there was a suggestion of a pleuritic rub heard in this area near the axilla.

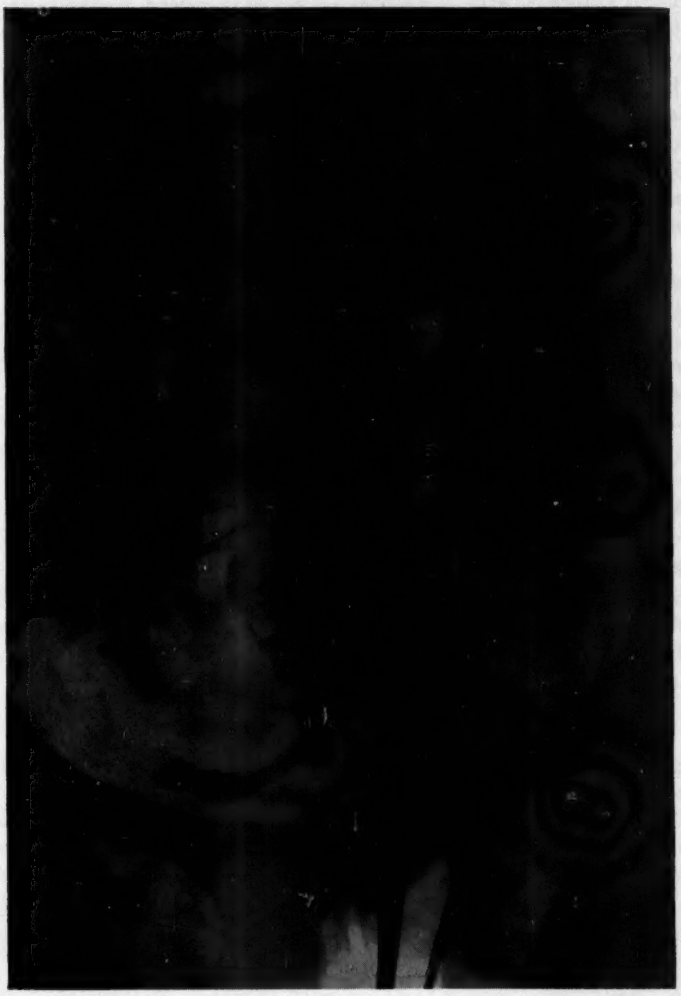

Fig. 1.

The abdomen and lower extremities were negative to inspection and palpation. The impression was that the patient had a pleurisy at the right axillary base with a possible pneumonitis. A roentgenogram taken the same day, Nov. 11, 1949, showed an irregular infiltration at the right base which suggested a pneumonitis or a possible pulmonary infarct. The blood count, Nov. 12, 1949, showed leucocytes 16,050, neutrophiles 78 per cent, lymphocytes 15 per cent, monocytes 7 per cent, hemoglobin 78 per cent (13 Gm.), red blood cells 4,080,000. The sedimentation rate (Westergren) was 68 mm. in 60 minutes. The Mazzini, urinalysis, blood culture, urine tests for fat globules and iodides were all negative. An electrocardiogram was negative particularly for acute cor pulmonale.

The patient was given penicillin 50,000 units every three hours intramuscularly. Codeine and acetyl salycylic acid were prescribed as necessary to control the cough, pain, and fever. Because of oil embolization of uterine venous plexus and left uterine vein she was placed on heparin and Dicumarol prophylactically according to the May procedure.

The patient continued to run a slight fever for five days, the highest point being 101° F.

Subsequent x-rays were reported as follows: on Nov. 18, 1949, "a definite extension of the process in the lower right lung and also a small amount of fluid in the right base"; on Nov. 25, 1949, "there is still some diminution of aeration in the right base although there is definite improvement and less evidence of pathology than on previous examination. There appears to be a small amount of fluid present but this is diminished in amount as compared to the previous examination."

The patient's clinical course continued favorable thereafter. The pain in the chest gradually abated. The cough which was always nonproductive lessened and finally cleared. She became asymptomatic.

Subsequent leucocyte counts were as follows: November 19, 9,150; November 25, 13,700; December 1, 6,400. The differential counts were essentially the same as that first noted. Other sedimentation rates were: November 19, 56 mm. in 60 minutes; November 25, 55 mm. in 60 minutes; December 1, 32 mm. in 60 minutes.

At the time of her discharge from the hospital on December 2, 1949, the patient felt perfectly well and had no complaints. The breath sounds were normal, and the dullness at the base of the right side of the chest was gone. A roentgenogram taken on Dec. 1, 1949, showed "the previously noted inflammatory process involving the lower portion of the right lung field has completely cleared, the only residual change being a slight clouding of the posterior portion of the right costophrenic sulcus which probably represents a slight residual pleural thickening."

The patient was discharged as improved on Dec. 2, 1949, and was returned to Dr. R.'s office for a recheck x-ray of the pelvis. The report states: "Scout film examination of the abdomen reveals a small amount of opaque material in the lesser pelvis and in both flanks. No evidence of opaque material is demonstrable in the blood vessels. The kidney and psoas muscle shadows appear normal. No abnormal intra-abdominal masses are observed."

A recent communication, March 31, 1950, from the patient indicates that she is entirely well at this time.

Reference

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PRIMARY CHONDROSARCOMA OF THE UTERUS

EDUARDO F. PEÑA, M.D., MIAMI, FLA.

(From the Jackson Memorial Hospital)

THE following is a report on a case which is outstanding in two respects: First, one is dealing with a very unusual tumor and, second, the case presents very impressively the well-known but still not wholly acknowledged fact that the metastases of a primary tumor, though originating from the same germinal layer, may bear no resemblance at all to the primary growth.

The patient, Mrs. D. L., came to my office on Sept. 22, 1948, with the complaint of vaginal bloody staining for the past month and severe metrorrhagia for the last 24 hours, accompanied by acute abdominal pain, backache, and frequency of urination. She appeared in distress due to acute anemia from hemorrhage and extreme nervousness.

The family history and patient's past history were irrevelant. Menarche had been at 16 years, periods 28 days, lasting 5 days. Menopause had been at the age of 48 years.

This 51-year-old patient had been married for 28 years, never used contraceptives, and never had any children.

Five years ago (at age 46) she had an episode of amenorrhea for 3 months. She visited a doctor who, without any vaginal or complete physical examination, explained to the patient that she might have the "menopausal changes." She was given phenobarbital and some other pills, apparently an oxytocic. A few days later she had severe uterine cramps, backache, vomiting, and what appeared to be an episode of menometrorrhagia. She had a regular menstrual period then with episodes of anemorrhea for as long as 3 to 4 months. At the age of 48 she apparently went through the menopause until the date of visit, suffering from metrorrhagia.

Physical examination was entirely negative except for the vaginal findings. Abdomen obese, no scars, tender to palpation, and exquisitely tender in both adnexal regions. A mass about 20 cm. in diameter was palpable through the abdomen, seemingly a uterine tumor. Vaginal examination was entirely normal except for the presence of large blood clots. The cervix appeared normal, nulliparous, and with a dilatation of the external os of about 1.5 cm. Bimanual examination of the uterus revealed it to be round and about 20 to 25 cm. in diameter.

A tentative diagnosis of carcinoma of the fundus was made and because of the severe and persistent hemorrhage the patient was hospitalized at once.

Laboratory examination revealed a 2,000,000 red cell count, 1,200 white cells, differential normal, color index of 0.9, and a 58 per cent hemoglobin. Urinalysis was negative.

Operation consisted of a total hysterectomy including tubes and ovaries. The uterus was about 20 cm. in diameter, perfectly round, and very friable. On attempt to grasp it with a tenaculum the walls tore and a moderate amount of gelatinous mucoid tissue exuded through the wounds.

The patient received about 2,000 c.c. of whole blood and left the operating room in good condition.

The uterus was opened longitudinally and disclosed a large mass about 14 cm. in diameter within the cavity and with no attachment to the uterine wall. It had an appearance of a collection of thousands of grains of substance resembling barley, rather

transparent, glass bead-like, perhaps myxomatous. In view of the possibility of the mass being a degeneration from some foreign body the tumor was opened and nothing was found.

The pathological tissue was studied by several pathologists at various institutions. The final diagnosis was: (1) chondromyxosarcoma of pedunculated fibroid; (2) multiple fibromas; (3) acute metritis; (4) chronic cervicitis. The pathologist considered the possibility of a mixed tumor of the endometrium. The patient made an uneventful recovery and a postoperative follow-up was normal.

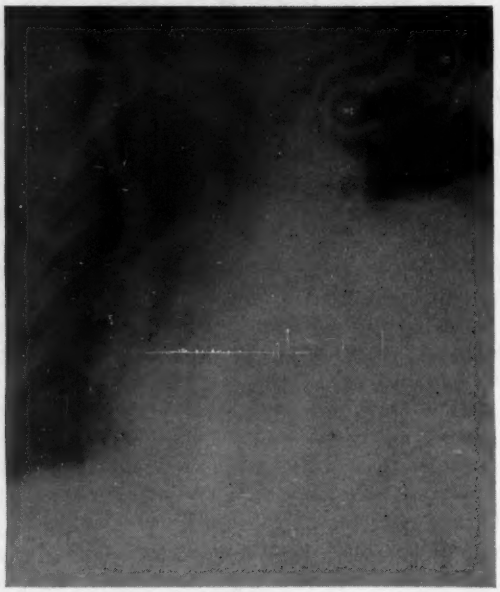

Fig. 1.—X-ray of chest, demonstrating the shift of the heart to the right and occupation of the anterior mediastinum and left pleural cavity by tumor masses.

Seven months later the patient appeared at the office complaining of pain in the left chest with dyspnea for the last 2 weeks. After clinical examination a tentative diagnosis of pleural effusion on the left chest was made. She was immediately hospitalized and x-ray studies showed an extensive amount of fluid filling almost the entire left pleural space and displacing the heart and mediastinum towards the right side. Daily x-ray films showed the amount of fluid increasing. A barium x-ray finally showed the esophagus displaced markedly to the right side by a tremendous mass involving the mediastinum and the entire left space. The appearance was of a mediastinal and left pleural neoplasm with fluid in the pleural space. No evidence of a primary mediastinal tumor was seen. Numerous laboratory tests including cultures, blood analysis, urinalysis, sputum analysis, pleural fluid analysis, etc., were done. No particular findings were obtained except for the typical changes of anemia. Pathological examination of the pleural cavity fluid was negative.

One month after admission to the hospital the patient died, most probably from metastases from the previously operated upon myxochondrosarcoma of the uterus.

At autopsy the mediastinum was found to be completely replaced by a very soft edematous tumor mass which invaded the lung and the pericardium in several instances. Independently a few tumor nodes of the same architecture were noted within the parenchyma of the lung. The pelvis at the site of the primary surgery revealed numerous cartilage-like implantations. Histologically the mediastinal tumor and the nodes in the lung consisted of a mesenchymatous tumor, the basic matter of which was extremely

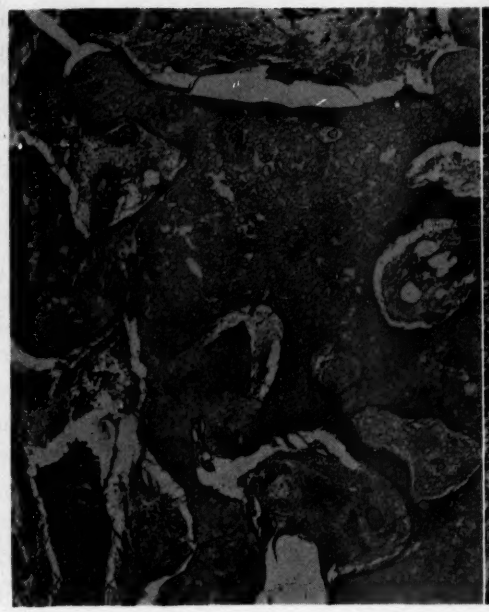

Fig. 2.

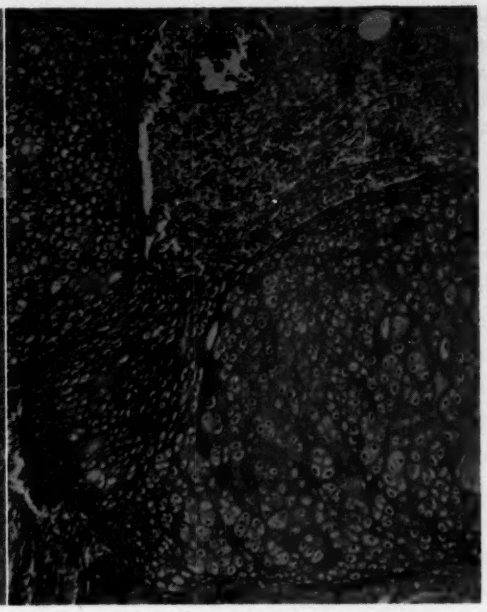

Fig. 3.

Fig. 2.—Microscopic aspect of the tumor of the uterine cavity, under low power, presenting irregular-shaped large plugs of tumor cells.

Fig. 3.—Same as Fig. 2, under high power, identifying these cells as cartilage-like tissue.

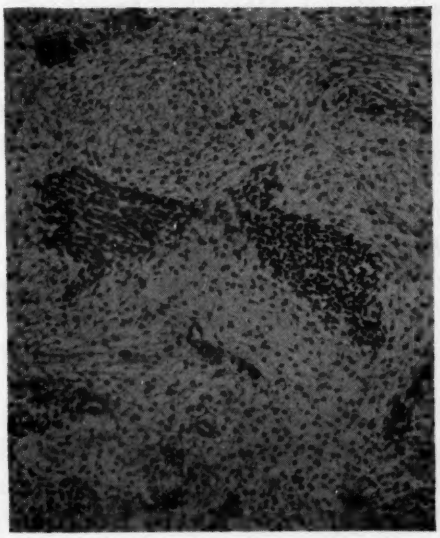

Fig. 4.—Primary site of the tumor in the uterine cavity, presenting invasion of immature cartilage tissue into uterine wall.

edematous, contained numerous neoplastic immature connective tissue cells as well as triangular-shaped cells producing delicate fibrils. In other areas, islands of extremely immature mesenchymatous tissue were present, very embryonic in character.

The histological examination of the implantations in the pelvis mentioned above were identical with the tumor tissue found in the surgical specimen. A careful recheck of the slides of the latter revealed not only that the primary tumor of the uterus con-

sisted of rather mature-looking cartilage but also that the latter invaded the myometrium in several places and gradually changed into a very embryonic mesenchymatous tissue exhibiting exactly the same features as were found in the lungs and mediastinum at autopsy. With these findings, the identity of both tumor developments, in the uterus and in the mediastinum, was well established.

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701 DUPONT BUILDING

Editorial

The American Board

When the plans for the organization of the American Board of Obstetrics and Gynecology were formulated in 1927, self-anointed and inadequately prepared specialists were numerous and there were pathetically few good obstetrical and gynecological residencies available. In many hospitals and medical schools the obstetrical and gynecological departments were completely separate units, and in some of the latter the gynecological service existed merely as a subdivision of the department of surgery. Since the societies that sponsored the Board believed that the intelligent practice of obstetrics depends in large part upon a thorough knowledge of gynecology, and vice versa, two of the chief objectives of the Board were to provide a means whereby a well-trained obstetrician and gynecologist could be distinguished and so designated, and to encourage the universal unification of obstetrics and gynecology, subjects which should be inseparably interwoven. It is now quite evident that during the past twenty-one years tremendous progress has been made in achieving those purposes. The Board has certified 3,136 diplomates to date, all of whom have a fundamental knowledge of both obstetrics and gynecology, regardless of the fact that some may limit their practice to one or the other. From the very inception of the Board, and often since then, suggestions have been made that unilateral certification in either obstetrics or gynecology might be desirable, and this question has been debated within the Board on many occasions. The final conclusion has always been that such a provision would seriously compromise the Board's efforts to encourage the training of all residents in both branches, either in combined or cooperating departments, a goal which it hoped might be reached in the not too distant future. Recently, however, efforts have been made indirectly, through the medium of extrinsic surgical organizations, to bring pressure to bear on the Board to accept as candidates for certification a small group who have had no obstetrical training, chiefly on the ground that they are qualified gynecological surgeons by virtue of their experience in abdominal surgery and their featuring the radical surgical treatment of pelvic malignant disease in their practices. The majority of this group have already been certified by the American Board of Surgery or are Fellows of the American College of Surgeons, or both, and it is difficult to understand how another certificate from the American Board of Obstetrics and Gynecology would endow them with any additional prestige. Despite the fact that no communication has yet been addressed directly to the Board, certain surgical societies have adopted resolutions and appointed committees, with the implied threat that if the American Board of Obstetrics and Gynecology fails to modify its regulations, a competing Board of Gynecological Surgery

will be organized. In 1935 the Advisory Board for Medical Specialists condemned dual certification except under exceptional circumstances, and then only with the consent of the original certifying Board. Since 1930 the American Board of Obstetrics and Gynecology has certified only one diplomate who held a certificate in urology, two who held certificates in surgery, and two who held certificates in radiology. Since 80 to 90 per cent of gynecological patients do not require surgical treatment, gynecology and pelvic surgery are certainly not synonymous terms. At the present time it is no more essential for every gynecologist to be qualified to perform a pelvic evisceration than it is for every general surgeon to be experienced in the removal of a cerebellar tumor. That the gynecologist must be capable of dealing with surgical emergencies in the lower abdomen in the female is conceded, and this the Board now requires. To clarify the atmosphere and eliminate any charge of unfair discrimination, the Board recently promulgated the following regulations:

"1. That physicians otherwise qualified, who were graduated before Jan. 1, 1939, and whose required training was in obstetrics or gynecology alone, and who have confined their practice to obstetrics or gynecology for at least five (5) years immediately prior to application be accepted for examination as candidates for certification in either obstetrics or gynecology. In all other respects requirements for eligibility remain the same for those physicians graduated since 1939. Bilateral training is required as published in the Bulletin of the Board.

"2. Applicants who have been certified by one of the other American Specialty Examining Boards will not be eligible for certification by this Board until they have relinquished the certificate previously conferred.

"3. Since the vast majority of obstetrical and gynecological cases are nonoperative, the Board requires adequate training in basic sciences, infertility, endocrinology, oncology, irradiation therapy, psychosomatic medicine, electrotherapy, and other nonoperative methods of diagnosis and treatment as well as training in major operative procedures."

Walter T. Dannreuther, M.D.

Department of Reviews and Abstracts

Selected Abstracts

Endocrinology

Netter, A., Mathe, G., and Pottier, R.: The Urethral Smear in Man, Ann. d'endocrinol. 9: 548, 1948.

The authors took urethral smears from 12 normal adult males, 4 male children, 5 untreated males showing clinical evidence of undeveloped genitals and 3 males who were treated for their undeveloped genitals with testosterone.

Smears from the fossa navicularis exhibit 6 principal types of cells: Grade I, large polygonal, anuclear cells comparable to the superificial vaginal cells (keratinized cells); Grade II, karyolitic cells, with eccentrically placed nuclear remnants, comparable to or exactly identical with the nucleated superficial squamous cells of the vagina Grade III, the intermediate cells whose nuclei occupy 20 to 50 per cent of the cell area. The size and shape of the cells are similar to those of Grades I and II above. The nuclei exhibit a fine reticular network of chromatin; Grade IV, cells whose nuclei occupy 50 to 80 per cent of the cell area. They are smaller in size, their protoplasm is more basophilic and more intense, and the nuclear chromatin shows more clumping; Grade V, basal cells whose nuclei occupy 80 to 90 per cent of the cell area; the chromatin is mottled with vacuoles. They resemble large lymphocytes; Grade VI, naked nuclei with dense cytoplasm.

In normal males the greater percentage of dominant cells are Type III. In male infants the greater percentage of cells are Type V. In untreated males exhibiting inadequate male hormone there is a marked predominance of Type IV cells. In undeveloped males treated with testosterone, one can observe a shift of type of cells during treatment with 400 mg. of testosterone from Types IV and V to Type III.

The authors conclude the navicular fossa of the male urethra appears to be an excellent indicator of androgenic balance and provides another method of evaluating the testicular activity of a given male patient.

C. E. FOLSOME

Thibault, Ch., and Soulairac, A.: Phosphatase Activity in the Mammalian Genital Tract. Experimental Modifications in the Female Rat, Ann. d'endocrinol. 9: 555, 1948.

The authors had previously shown the existence of an alkaline phosphatase activity in the genital tract of the male. This activity was probably related to the glucose metabolism and the motility of spermatozoa. The writers hypothesized that this phosphocatalytic response depended primarily upon the testicular hormone. Because the histochemical studies of Gomori and Atkinson and Elftman on the uteri of dogs and sows showed also the presence of alkaline phosphatase, the authors decided to extend their study to the female.

The writers injected 15 gamma of folliculin in 72 hours and restored normal vaginal phosphatase activity. The normal activity of the uterine horns was obtained only when one injectetd 5 mg. of progesterone *after* the folliculin. They found the progesterone action thus was specific since its replacement by 5 mg. of testosterone or 5 mg. of desoxycorticosterone did not restore phosphatase activity.

The authors conclude, contrary to Atkinson and Elftman's sow studies, that the phosphatase activity of rat uterus appeared after castration and disappeared during the re-establishment of an experimental endocrine cycle. Six photomicrographs and one table accompany the article.

C. E. FOLSOME

Endometriosis

Meleiro de Sousa, Henrique: Heterotopic Endometriosis, Rev. Clin. do. Instituto Maternal 2: 19, 1949.

The author, chief of the gynecological service of the Alfredo da Costo Maternity Hospital in Lisbon, reports on his series of 35 cases of heterotopic endometriosis before the 1948 Second Portuguese-Spanish Congress of Obstetrics and Gynecology. These 35 cases were encountered during the year of 1947 among 287 operative gynecologic cases, an incidence of 12.0 per cent. They represent 26.9 per cent of the actual laparotomy cases, 130 patients. Among the 82 uteri removed and examined histologically heterotopic endometriosis was found in 32 cases, 39.0 per cent.

In 60 per cent of the 35 cases, the patients gave a history of progressively increasing degree of symptomatology from menarche up to the period for surgical indication which fell in between the fourth and fifth decades of life. The more frequent symptoms included menorrhagia, menometrorrhagia, pelvic pain, and dysmenorrhea. Dysmenorrhea occurred more frequently in the younger patients—as primary dysmenorrhea in 70 per cent of the patients and secondary dysmenorrhea in the remaining 30 per cent whose ages were between 20 and 40 years.

Relative infertility and a prolonged menstrual period appeared in about one-half of the patients under the age of 40 years and half of the series in women between the ages of 30 and 40 years. All cases were treated with conservative surgery in so far as possible, viz, 11 total hysterectomies and 15 subtotal hysterectomies with variable adnexal conservative surgery. In 17 patients the following associated pathologic conditions were present: follicle cysts of ovary in 6 cases; hemorrhagic luteal cysts of ovary in one case; paraovarian cyst in one case; endometrial hyperplasia in 4 cases; tuberculosis of the endometrium in one case; chronic salpingitis in 3 cases, and carcinoma of the Fallopian tube in one case. In 27 cases the endometriosis was confined to the uterus; to the ovary in 2 cases; to the tube alone in one case; to uterus and ovaries in 4 cases and once to the uterus and tubes. There are no tables, graphs, or illustrations.

C. E. FOLSOME

Gynecology

Ingelman-Sundberg, Axel: The Pubovesical Ligament in Stress Incontinence, Acta obst. et gynec. Scandinav. 28: 185, 1949.

The known facts concerning the anatomy of stress incontinence in the female are reviewed, and it is stated that the basic lesion is ptosis of the bladder during urination, caused by relaxation of the pelvic floor, and resulting in increased tension on the pubovesical ligament. Theoretically, the elimination of this tension by surgical division of the pubovesical ligament might relieve the stress incontinence. An operation based on this assumption is described. The procedure consists of incising and bluntly dissecting the pubovesical fascia through a median suprasymphyseal incision. The operation was successful in relieving the stress incontinence of four patients who had remained incontinent following anterior colporrhaphy or bladder suspension.

DOUGLAS M. HAYNES

Wagner, Helmut: Interstitial Hemorrhage From a Ruptured Krukenberg Tumor With Virilism, Zentralbl. f. Gynäk. 72: 300, 1950.

The case history is presented of a para i, gravida i, who, after 29 years of normal feminine existence, developed during a period of 6 months an intra-abdominal mass together

with marked masculinizing symptoms. This patient experienced a sudden catastrophic intra-abdominal hemorrhage. On operation, bilateral Krukenberg tumors were found, one of which showed extensive carcinomatous infiltration of a large blood vessel. The diagnosis was confirmed microscopically after hysterectomy and bilateral salpingo-oophorectomy had been performed. Differential diagnosis on the basis of developing and acute symptoms lay between the correct pathologic condition and ruptured ectopic gestation. In the discussion, the author propounds the theory that the virilism which developed was due to the lack of production of female sex hormone resulting from tumor growth, which, in turn, allowed unopposed activity of male hormone produced by the adrenal cortex.

L. B. WINKELSTEIN

Hengstmann, H. and Wittekind, D.: Experience With Cytologic Tumor Diagnosis by the Papanicolaou Method, Med. Klin. 45: 463, 1950.

The authors describe the Papanicolaou technique in detail, and compare it with their experiences with May-Grünwald, Giemsa, and hematoxylin-eosin stains. They point out that neither the dyes used, nor the wet-fixation method employed are new developments, nor are any new characteristics of tumor cells revealed. The advantages of wet-fixation are better preservation of tumor cell nuclei, lack of staining of extracellular material, and hence better transparency of the slides. The latter factor permits better visualization of the nuclear membrane.

A simplified counterstain with eosin or lichtgruen is recommended to replace the complicated Papanicolaou plasma counterstain.

IRVING L. FRANK

Sered, Harry, Falls, Frederick H., and Zummo, Bruce P.: Streptomycin in Gynecologic Tuberculosis, J. A. M. A. 142: 547, 1950.

The authors report 16 cases of genitoperitoneal tuberculosis. These patients were subjected to streptomycin therapy for 6 to 8 weeks, operated upon, and given another three-week course of treatment with the drug postoperatively. At the outset 2 Gm. of streptomycin were used daily but with the onset of vestibular symptoms this was reduced to 1 Gm. per day. All receiving the drug showed some clinical improvement and when the drug was given 6 to 8 weeks preoperatively there seemed to be fewer technical difficulties encountered in the operation. In this study total hysterectomy was the surgical procedure in 13 cases, subtotal hysterectomy in 2 cases, bilateral salpingo-oophorectomy in one. Total hysterectomy and bilateral salpingo-oophorectomy are advised wherever ovaries are involved, with primary closure of the vagina and abdominal wall, and total hysterectomy and at least bilateral salpingectomy should be performed whenever tuberculous peritonitis is found, if the patient is a good surgical risk. Those patients with lesions elsewhere may require streptomycin for longer periods postoperatively. The only complication in this series occurred in one patient who became streptomycin fast and subsequently died.

WM. BERMAN

Gynecologic Operations

Werner, P.: Vaginal Salpingectomy for Tubal Pregnancy, Wien. klin. Wchnschr. 62: 248, 1950.

Operation by the vaginal route is offered as the method of choice for cases of tubal pregnancy in which (a) the palpable mass is not larger than a hen's egg, (b) a diagnostic colpotomy has been necessary, and local findings seem to permit proper exposure, and (c) there is no active intraperitoneal bleeding.

Through the posterior colpotomy wound, the size and position of the mass are determined digitally. After appropriate dissection, an anterior colpotomy is then created, through which the tubal mass is delivered into the vagina and ablated. The tubal stump is then

affixed to the margin of the anterior colpotomy incision, a procedure which would make any secondary tubal hemorrhage extraperitoneal, prevent intra-abdominal adhesions, and correct pre-existing retrodisplacement of the uterus. The two colpotomies are then closed around intraperitoneal drains.

The suggested postoperative advantages of this operation are reduced pain, freer ambulation, and earlier return of intestinal activity. The author has performed 38 operations of this kind; in which series there were 5 cases of ruptured tubal pregnancy, and 33 cases of unruptured tubal pregnancy or tubal abortion.

IRVING L. FRANK

Labor, Management, Complications

Prytz, Dan: Contriction Ring Dystocia, Acta obst. et gynec. Scandinav. **29:** 304, 1949.

Five cases of constriction ring dystocia occurring in a series of 3,200 labors are reported. All five patients had received oxytocic drug for stimulation of desultory labor; in addition, morphine had been administered to two of them. Two cases in which the fetus succumbed terminated in embryotomy; two deliveries were effected by forceps, preceded in one instance by digital dilation of the constriction ring; and one case, reported in detail, was that of a neglected twin delivered by high forceps operation under ether anesthesia supplemented by amyl nitrite.

The concept is presented that a constriction ring is the expression of tetanic muscular contraction incident to fatigue. It tends to occur in conjunction with fetal malposition, with contracted pelvis, in the elderly primigravida, and following the use of drugs to stimulate labor. Underlying causes include premature rupture of membranes, intrauterine manipulations, and uterine dyskinesia. The fetal mortality has been variously reported from 5 to 85 per cent.

Management may be conservative or radical. The former implies heavy sedation, usually with morphine; maintenance of fluid balance; and control of infection. The latter consists of operative intervention with the aid of deep anesthesia supplemented by a powerful antispasmodic: epinephrine, magnesium sulfate, or amyl nitrite. The author favors the latter drug, which was introduced for this purpose by Gilliatt; it is simply administered, has few contraindications, and was effective on the single occasion on which he used it.

DOUGLAS M. HAYNES

Ingerslev, Mogens: Løvset's Method of Delivering the Arms in Breech Presentation, Acta obst. et gynec. Scandinav. **28:** 189, 1949.

Løvset's method of delivering the arms in breech presentation is evaluated by the author following his use of it in 13 difficult breech deliveries. The rationale of the maneuver rests on the fact that, because of the inclination of the pelvic inlet and pelvic axis, the posterior shoulder of a fetus presenting by the breech tends, at any given moment during extraction, to be nearer the inlet than the anterior shoulder. If slight traction is applied to the breech while the fetus is rotated 180 degrees with the back upward, the originally posterior shoulder will stem under the symphysis and be readily delivered; rotation back to the original position will then similarly simplify delivery of the other shoulder. The author applied the maneuver in cases in which disengagement of the arms presented difficulty. In 9 of the 13 cases, the arms were extended alongside the head; and the maneuver was found to be especially useful in this contingency. In five cases, the method was helpful in relieving impaction of the fetal body after delivery to the scapulae. The only objection to the use of the method is the necessity for simultaneous rotation and traction; traction must be made firmly, evenly, and with great gentleness. If there is appreciable resistance, it is best to desist, and to attempt rotation in the opposite direction.

DOUGLAS M. HAYNES

Miscellaneous

Arzac, Jose P., and Velez, Oropeza.: Effect of Hypothyroidism on Ovary Transplanted Into the Anterior Chamber of the Rabbit Eye, Ginec. y obst. México 3: 413, 1948.

In a well-controlled animal study at the Endocrine Laboratory at the Spanish Hospital the authors placed ovarian fragments as homologous grafted transplants into the anterior chamber of the rabbit's eye. They observed that in hypothyroid thiouracil-fed animals the number of maturing follicles and increase in the size of the graft were greater than in control animals. Corpora lutea were also found developed in the transplants from 5 to 35 days after administration of the drug. The appearance of the *Blut-punket* were relatively seldom seen in the thiouracil-fed castrated animals, while it was the rule in the castrated non-treated females. The authors document their fine data well into three tables and three figures. Further they objectively consider some of the difficulties and problems involved in this interesting and well-reported study.

C. E. FOLSOME

Dahle, Thor: The Effect of Pituitrin, Pitocin and Pitressin on the Activity of the Human Uterus, West. J. Surg. 59: 168, 1950.

Extracts of the posterior pituitary gland produce oxytocic effects upon the human myometrium in the pregnant, nonpregnant, and puerperal uteri. Of the two fractions in the posterior pituitary lobe, Pitressin is more oxytocic to the human myometrium than Pitocin. Pitocin rarely has any, and, at most, a very weak oxytocic effect upon the nonpregnant myometrium, and upon excised muscle strips. It is completely without effect even upon strips removed from puerperal uteri. Pitressin is consistently oxytocic to all excised muscle strips. The human myometrium in vivo responds strongly to Pitressin throughout the menstrual cycle but its maximum effect is seen in the postovulatory phase. It is likewise oxytocic to the pregnant uterus during the first trimester. There is general agreement as to the reaction pattern to Pitressin whether the uterus be in vivo or strips of the same uterus be removed immediately following the observations made while the uterus was intact.

The in vitro studies were made upon 61 uterine muscle strips from a like number of patients. Pituitrin caused positive reactions characterized by increased frequency of contraction, increased tonus, and hyperirritability. The administration of progesterone in a dose of 10 mg. a day for three consecutive days prior to the hysterectomy which provided the source of the muscle strips did not alter the in vitro response to Pituitrin or Pitressin. It is concluded that Pitressin is more oxytocic than Pitocin whether the study be made on excised strips or the uterus in vivo. Pitocin was the more oxytocic upon the human myometrium only during the last trimester of pregnancy and the immediate postpartum period.

WILLIAM BICKERS

Hahn, Heinrich: The Facilitation of Cytologic Diagnosis of Carcinoma of the Female Genital Tract According to the Vaginal Smear Method in the Menopause by Previous Treatment With Follicle Hormones, Zentralbl. f. Gynäk. 72: 294, 1950.

The cytological picture of the vaginal smear is the physiological result of the exfoliation of cells from the superficial layers of the female genital tract. These smears, when studied by the Papanicolaou technique, show marked variations, which are the result of changes in the level of ovarian hormone secretion, and are so specific that they can be used for assaying levels of ovarian function. The study of vaginal cytology is also an excellent method for determining early malignant changes in the female genital tract. In certain instances (menopause, senile vaginitis) the upper cornified layers of the vaginal epithelium are absent due to lack of estrogen stimulation, and cells are proliferated from the lower basal layers. These cells, when examined in the smear, are morphologically similar to carcinomatous cells since they are immature and show signs of rapid growth. These carcinoma-like cells are often found where no hystological or clinical changes are noted. The author has shown that the

differential diagnosis of carcinoma can be facilitated by the administration of estrogens in doses of 2.5 mg./day for one week. This hormonal stimulation results in cornification of superficial layers, with subsequent disappearance of pathological cells from the smear. Thus, if no carcinoma is present, a normal smear is obtained, whereas, with true cancer, this improvement is not noted. Thus many doubtful cases can be cleared up in a period of seven days.

L. B. WINKELSTEIN

Cheval, M. M., and Hans, M. J.: Chemical Diagnosis of Pregnancy by the Determination of Histidine in the Urine, Bull. Assoc. d. gynéc. et d'obst. de lang. franç. 1: 7, 1949.

The authors redescribe the 20-minute chemical test by which pregnancy can be detected through the determination of histidine in the urine specimen. The first morning urine specimen is used. The specific gravity is brought between 1.010 and 1.005; a 10 per cent solution of barium chloride is added, drop by drop, after which a 5 per cent potassium permanganate is added until the precipitate has a rosy tint, then filter. To 5.0 c.c. of the clear solution add several drops of a 2.5 per cent solution of bromide containing 33 per cent acetic acid —about 10 or 12 drops as a rule—and wait ten minutes. Heat the test tube then up to 50° C. after which is added, drop by drop, a 3 per cent ammonium carbonate in diluted ammonia (2 to 1) solution. If histidine is present the solution turns from a rosy to a red wine color.

In a series of 23 patients, pregnant from 2 to 6 months, the test was found positive in all cases. There were 4 additional false positive cases. The writers report the histidine content in the urine can be elevated just before menstruation and exaggerated in fibroid cases. It rapidly disappears in toxemias and this finding alone may have real diagnostic value.

C. E. FOLSOME

Venereal Diseases

Lipp, Robert G., and Bibby, Douglas E.: Genital, Extragenital and Skeletal Granuloma Inguinale, West. J. Surg. 59: 173, 1950.

Granuloma inguinale may manifest itself by extragenital lesions and even visceral lesions. Skeletal involvement has been reported in 12 cases. The authors report here a case of osteomyelitis in which the Donovan bodies of granuloma inguinale were demonstrated. The patient was a Negro woman who complained of a profuse, foul, greenish yellow vaginal discharge. Small papular lesions over the labia had been noticed some months previously along with an enlarged lymph node in the right inguinal region. The serology was negative for syphilis. On examination the labia were covered with small tender ulcerating friable lesions with sharp and demarcated elevated borders. The right tibia midway on the anterior surface showed an elevated tender nodule 3 cm. in diameter which had ulcerated and was exuding a serosanguineous discharge. From this lesion on the tibia as well as lesions from the vulva the Donovan bodies were demonstrated. Treatment with streptomycin was initiated and response to treatment was very satisfactory.

WILLIAM BICKERS

Correspondence

The Speck Tubal Patency Test

To the Editor:

I have read with interest Dr. Rosset's article in the October issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, entitled "Experiences With PSP Tubal Patency (Speck) Test," and I should like very much to make a few comments.

I am appreciative of Dr. Rosset's interest in the test, but I question the approach of his investigation. I had considered his method, but discarded it, for I felt it would not give us the true evaluation of the test. He performed the test on tissue of a pathological nature which even Dr. Rubin finds to be a contraindication to the insufflation test (I. C. Rubin: Uterotubal Insufflation, St. Louis, 1947, The C. V. Mosby Company). It would have been interesting if Dr. Rosset had done Rubin tests and hysterosalpingograms along with the PSP in order to compare the results.

The eleven "erroneous" results are worthy of consideration. "Three cases with tubal patency" gave equivocal or negative results. One patient was described as having "huge fibroids," the other two were not described. The patency of the tubes were stated but no other proof given. Three gave positive PSP results but the tubes were considered closed *completely* because one had bilateral hydrosalpinx, another had a previous bilateral salpingectomy and the third had a left hydrosalpinx and a previous right salpingectomy. It would have been of interest to have done CO_2 insufflation or hysterosalpingography, for I have seen Lipiodol spilled over into the peritoneal cavity with bilateral hydrosalpinx. Another patient of mine had a Pomeroy tubal ligation and gave a positive PSP test which on laparotomy revealed a small opening along the mesenteric border of the tube. Therefore, the mere presence of hydrosalpinx or salpingectomy does not mean that there is no continuity between uterine cavity and peritoneal cavity. What about the pregnancies following salpingectomies and even hysterectomies (supracervical)?

Finally, "the remaining five cases represented blocked uterotubal systems" with positive PSP tests. One had bilateral hydrosalpinx follicularis, two had bilateral hemosalpinx, and one had bilateral grossly dilated blocked tubes. The fourth "specimen (totally removed uterus and tubes) was vigorously injected with methylene blue solution *in the laboratory* without any material appearing through the distal ends of the tubes." None of these five cases are sufficient proof in themselves that there was complete nonpatency of the tubes or complete lack of continuity between the uterine cavity and the peritoneal cavity.

Dr. Rubin himself admits that the CO_2 insufflation test is not infallible. On page 147 of his recent book, *Uterotubal Insufflation*, under the heading "Source of Error," he writes: "It is highly probable that in a number of instances tubes have been reported as non-patent only because they had not been insufflated at the time of physiological patency. In my experience, both with CO_2 insufflation and with the injection of radiopaque substances into the uterus, there are instances in which one or both uterotubal functions are resistant at certain times and patulous at others."

It would be presumptuous of me to believe that the PSP tests would ever supplant the Rubin test or hysterosalpingography. Yet if it were as accurate as these tests, then it would be a valuable tool for the study of fertility, for the gross evaluation of tubal patency could be done by more practitioners who are interested in the problem. Well-trained investigators of sterility are not available to all people as yet. In addition, insufflation using air is still being done and is exceedingly dangerous. Hysterosalpingography is expensive and requires the use of x-ray equipment. Therefore, I have felt that if a large series of cases were

performed comparing the results of the PSP test with either the Rubin test or hysterosalpingography or both—then and only then would the accuracy of the PSP test be known. They should be performed on sterility-problem patients, not on operative patients who are known to be diseased. This is the approach I have followed and have found the correlation between the tests to be excellent (J. A. M. A. 143: 357, 1950).

I have been interested in Dr. Israel's usage of quantitative determination of the urinary content of PSP which may be of use in evaluating an equivocal result, when the tubes are diseased. The quantitative return of the dye may be as useful as the degree of pressure in the Rubin test in determining the bore of the tubes.

GEORGE SPECK, M.D.

ARLINGTON, VA.
NOVEMBER 7, 1950

Reply by Dr. Rosset

To the Editor:

The privilege of reading and commenting upon Dr. Speck's letter is appreciated. The purpose of my investigation was to note the reliability of the PSP Tubal Patency Test in the presence of pathologic uteri and tubes. It is important in evaluating any recommended procedure to learn its limitations.

Dr. Speck's contention that one would not ordinarily select patients who have gross adnexal disease for testing is certainly correct. It is conceivable, however, that such pathologic tubes may not be palpable at all times. It was, therefore, of interest to learn that in hydrosalpinx, etc, the dilated tube (occasionally thin walled and occasionally thick walled) could be responsible for a false positive PSP test.

I was glad to note that Dr. Speck agrees that an inexact end point (equivocal) may exist.

E. M. ROSSET, M.D.

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NOVEMBER, 20, 1950

Pregnancy and Brain Tumor

To the Editor:

The instructive paper, "Eclamptic Manifestations Occurring in Pregnancy Complicated by Brain Tumor," by Drs. John R. Gregory and Gordon Watkins Douglas, published in the December, 1950, issue of the JOURNAL, very properly calls attention to the uncommon but confusing combination of brain tumor and pregnancy.

It should, perhaps, be emphasized that *any* intracranial space-taking lesion, not necessarily a neoplastic one, may give rise to the clinical picture of eclampsia. Dr. Bernard J. Alpers and I reported the rather sudden occurrence of edema, hypertension, albuminuria, severe headache, and generalized convulsions in a woman during the thirty-second week of pregnancy ("Eclampsia, Cerebral Abscess and Hemorrhage," the JOURNAL 47: 551, 1944). The illness was regarded as eclampsia until the postpartum appearance of coma which forced the consideration of a cerebral lesion upon us. This diagnosis could not, however, be substantiated clinically by any localizing signs. Post-mortem examination revealed the presence of a pneumococcic cerebral abscess surrounded by an area of fresh hemorrhage. Our patient, in contrast to the one observed by Drs. Gregory and Douglas, did not show the pathological changes in the liver and kidneys attributed by some to eclampsia.

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JANUARY 1, 1951

Necrology

GEORGE GRAY WARD, M.D., Fellow of the Royal College of Obstetricians and Gynaecologists (Hon.), well-known gynecologist of New York, died there Dec. 21, 1950, at the age of 82. Born in London in 1868, he came to this country in 1874, received his early education in Brooklyn and graduated from the Long Island College of Medicine in 1891, subsequently spending two years in postgraduate studies in Berlin, London, and Paris. Beginning practice in New York, he was made professor of gynecology at the Postgraduate Medical School in 1905, and held this post for eleven years, serving likewise as Secretary of the Faculty. Dr. Ward became professor of obstetrics and gynecology at the Cornell University Medical College in 1916, and was made emeritus professor in 1934. In 1918 he was called to the Woman's Hospital as Surgeon-in-Chief and remained there in this capacity until his retirement a few years ago. Major and Surgeon of the 12th Regiment, New York National Guard, he served as a volunteer during the Spanish-American War.

Member of numerous societies, he was a former president of the American Gynecological Society, the New York Obstetrical Society, the Medical Society of the County of New York, and a consultant in gynecology in numerous hospitals as well as a founder of the American College of Surgeons.

Dr. Ward participated in the founding of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY and served as a member of its Publication Committee for many years.

Item

The Institute of Cancer Cytology, Inc.

This organization has been formed to make available plans for the diagnosis of cancer by cytologic tests in the office of physicians. A mailing technique has been devised for specimens to be examined at constituted centers as well as an expanded educational and training program. The President of the Institute is Dr. Arthur P. Stout, Professor of Pathology, Columbia University, New York, and the Executive Secretary, Dr. K. Sheldon MacLean, 135 East 65 Street, New York, from whom further information may be obtained.

Erratum

In the article, "Sickle-Cell Disease and Pregnancy," by Woodard D. Beacham and Dan W. Beacham, in the December issue of the JOURNAL, the fifth sentence in the second paragraph on page 1224 should read, "Although she had a major complicating disease and probably had S.C.D. over a period of years, as indicated by the 3-Gm. spleen, the pathologist did not deem the death directly due to S.C.D. since massive pulmonary thrombosis was present."